

Materials Horizons: From Nature to Nanomaterials

Musarrat Husain Warsi
Rishabha Malviya *Editors*

Biopolymers

Green and Sustainable Approaches
for Drug Delivery, Food Products and
Packaging



Springer

Biopolymers

Materials Horizons: From Nature to Nanomaterials

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Musarrat Husain Warsi · Rishabha Malviya
Editors

Biopolymers

Green and Sustainable Approaches for Drug
Delivery, Food Products and Packaging



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Foreword

The growing global awareness of environmental degradation, climate change, and the unsustainable use of synthetic materials has resulted in a significant shift towards biopolymers, which are naturally derived polymers that provide safe, sustainable, and biodegradable alternatives to traditional petroleum-based products. This book, edited by Dr. Warsi and Dr. Malviya, offers significant insights for academic researchers, industrial professionals, and industrial experts interested in biopolymer development. The book covers all aspects of biopolymer production, from raw material sources and formulation science to cutting-edge applications and regulatory considerations.

The book's strength lies in its multidisciplinary approach, which incorporates the most recent breakthroughs in material science, pharmaceutical technology, biotechnology, food science, and artificial intelligence. It discusses key areas such as nano-formulations, oral and parenteral drug delivery, protein and peptide transport, crosslinking technologies, and gene delivery, which have the potential to revolutionise therapeutic strategies by increasing bioavailability, lowering toxicity, and enabling targeted, controlled release.

The book also explores developing technical concepts such as 3D and 4D printing, which are fast transforming personalised medicine and biomedical implants. It also takes a pioneering approach to the convergence of artificial intelligence and sustainable biopolymer production, which is becoming increasingly important for expediting research and optimising formulation techniques.

Beyond pharmaceuticals, the book includes insightful and well-researched chapters on the application of biopolymers in the food sector and packaging materials. Chapters on food waste valorisation, agro-residue-derived biomaterials, and biodegradable packaging solutions make significant contributions to the broader sustainability discussions.

Under the dynamic editorial strategy of Dr. Warsi and Dr. Malviya, this book integrates current knowledge and forecasts future trends, establishing it as a benchmark reference in the field. In fundamentals, the book *Biopolymers—Green and Sustainable Approaches for Drug Delivery, Food Products and Packaging* is more than just a compilation of scholarly publications; it also serves as a road map for the future of sustainable materials research.



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Preface

The global community is increasingly recognising the importance of sustainable, environmentally friendly technologies in a variety of fields. Biopolymers, or sustainably generated polymers, provide an environmentally acceptable alternative to synthetic materials. These biodegradable and biocompatible materials are driving research and development in medicines, food science, packaging, and biomedical engineering.

The book *Biopolymers—Green and Sustainable Approaches for Drug Delivery, Food Products and Packaging* serves as a comprehensive and multidisciplinary exploration of the ever-expanding field of biopolymer applications. It starts with a fundamental understanding of biopolymers and their evolutionary function in biomedical sciences, laying the foundation for more in-depth research into source materials, extraction methods, and processing techniques. The book classifies biopolymers according to their animal and plant origins, emphasising their unique chemical features, functionality, and appropriateness for biomedical and industrial uses.

A substantial part of the book is dedicated to the pharmaceutical and healthcare industries, where biopolymers are rapidly being used in drug delivery mechanisms. Topics such as crosslinking techniques, implantable devices, gene therapy, and smart medication delivery systems using 3D and 4D printing demonstrate the cutting-edge nature of continuing research and innovation in this field.

The book further explores the use of artificial intelligence in the design and optimisation of biopolymer systems, aiming to accelerate the fabrication of next-generation biopolymers with tailored features for specific applications. In addition to healthcare, the book provides valuable insights into the food and packaging industries, focusing on the use of biopolymer-based materials in food product formulations, biodegradable packaging, and sustainable composite materials.

This book explores the use of biopolymer-based materials in food product formulations, biodegradable packaging, and sustainable composite materials. It also explores the conversion of food waste and agricultural residues into functional biopolymers, highlighting waste valorisation and sustainable innovation. The book also addresses intellectual property rights, regulatory concerns, and the commercial viability of biopolymer technologies. The book is a result of a collaborative effort,

with gratitude to all contributing authors, peer reviewers, academic institutions, and research organisations. The hope is that the book inspires readers to pursue innovative research, encourages interdisciplinary collaboration, and contributes to the development of green technologies, aligning with global sustainability, health, and environmental stewardship goals.

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About This Book

Biopolymers are emerging as a key solution to the growing need for sustainable materials across industries. This book explores the synthesis, characterisation, and application of biopolymers that originate from natural sources, with a particular emphasis on their integration into cutting-edge drug delivery systems, food items, and sustainable packaging technologies.

Biopolymers were utilised in biomedical sciences, establishing foundations for their growing importance in modern healthcare. The book provides methodical insights into biopolymers derived from plants and animals, emphasising their molecular structures, extraction methods, sources of raw materials, and biocompatibility. The application of biopolymers in gene delivery systems, implantable medical devices, parenteral and drug delivery, crosslinking techniques, and next-generation technologies like 3D and 4D printing for tissue engineering and personalised medicine is also included.

Using artificial intelligence to design, develop, and optimise sustainable biopolymer systems is a novel aspect of the book. AI technologies speed up the production of innovative bio-based solutions with better performance and a smaller environmental impact by enabling predictive modelling, material screening, and design automation. Considering the practical uses of biopolymers in food products, biocomposite materials, and environmentally friendly packaging, the book extends its focus beyond the biomedical and pharmaceutical domains to include the food industry. It covers the issues of scalability, material performance, and regulatory compliance in biopolymer-based food packaging, presenting real-world examples for industrial application.

The book also addresses regulatory frameworks, patents, and potential future paths for biopolymer technology commercialisation. For those working in pharmaceutical sciences, materials engineering, polymer chemistry, food technology, green biotechnology, industrial scientists, researchers, academicians, and environmentalists, this book is a priceless resource.

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Chapter 1

Biopolymers: An Overview and Progressive Phases in Biomedical Sciences

Sudipta Choudhury , Shivaswamy Umamaheshwari,
and Kanthesh M. Basalingappa 

Abstract Biopolymers are naturally occurring polymers from living organisms such as bacteria and plants, offering a green and sustainable option compared to traditional petroleum-based polymers. Chain molecules composed of repeating chemical units from renewable sources, being biodegradable and non-toxic, are attracting attention as biopolymers. Biopolymers are exploited to minimize dependence on non-renewable sources and reduce pollution by synthetic materials. They are non-toxic and biodegradable, hence promising candidates for application in a wide range of fields, particularly pharmaceuticals and biomedical sciences. The chapter addresses the elementary characteristics of polymers and biopolymers and their application in biomedical applications such as wound healing, drug delivery, and tissue engineering. For biomedical applications, the material ought to be biocompatible, degradable to non-toxic products, possess low antigenicity, and high bioactivity, induce cell growth and proliferation, and be processable into complex shapes with appropriate porosity and appropriate mechanical behavior. In addition, processability into complex shapes with appropriate porosity and appropriate mechanical behavior are crucial factors. The chapter gives an overview of biodegradable biopolymers and their significance in biomedical applications. The most accessible and prevalent biopolymers are addressed, with emphasis on their characteristics and biomedical innovation potential.

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Keywords Biopolymers · Drug delivery · Tissue engineering · Wound healing · Biocompatibility · Bioactivity

1 Introduction to Biopolymers

The global output of synthetic polymers is estimated at 140 million tons on an annual basis. Since polymers are remarkably enduring, they can persist within the biosphere indefinitely due to their slow degradation cycles. The pollution of the environment by synthetic polymers, including plastic waste and water-soluble synthetic polymers found in sewage, poses a significant challenge. Plastics and polymers form an essential part of our daily life. However, their accumulation in the environment results in these materials being stored in landfills at about 8% by weight and 20% by volume [1]. Recently, there has been an increase in efforts aimed at protecting the environment through the use of renewable natural materials as well as materials that biodegrade naturally. The fields of biorespecting therapeutic polymer systems and materials are some of the most appealing fields in polymer science. There is increasing interest in the limited-time therapeutic applications of bio-assimilated polymeric compounds [2]. Biopolymers represent a class of polymers synthesized by all living organisms. Examples include anionic polysaccharides like alginate and carrageenan, which are derived from seaweeds, and chitosan, sourced from the exoskeletons of crustaceans as well as the shells of certain fungi, algae, and yeast [3, 4].

Biopolymers are typically considered to be sustainable and renewable materials, formed from living (plant) material capable of being grown indefinitely. Biopolymers are responsible for an astonishing array of functions in our body; they create the glue that binds cells together into tissues, they emit subtle chemical signals that cells replicate in their behavior, they nurture the hydration and pliability of the skin, they lubricate our joints and our guts, they nurse our cornea to crystal clarity, they pack our bowels with mucus gel to fight off pathogens that we inevitably inhale. These biopolymers have significant characteristics like antibacterial activity, biodegradability, and biocompatibility. Naturally occurring microorganisms like bacteria, fungi, and algae degrade biopolymer fast. Thus, biopolymers can be derived from some natural base materials such as sugar, cellulose, starch, and fossil oil [6].

The chemical structures and compositions of biopolymers are very similar to those of native extracellular space macromolecules. When applied in situations where enhanced functionality and value addition are the benefits, biopolymers' advantages over plastics are incomparable. The use of these substances in a biological system would most likely reduce the toxicity, immunological response, and persistent inflammation that are usually observed following the introduction of a synthetic polymeric device into the host. Moreover, in some particular applications, the mechanical and electrical properties needed can be provided by chemically modifying the biopolymers [7].

2 History and Importance of Biopolymers in Nature

Over the centuries, countless materials have been studied and used for clinical therapeutic intervention. The resources are mostly selected based on our relative understanding of their features and what was readily accessible. It is difficult to date exactly when people started to use biomaterials. Between 1914 and 1918, there was a development of new metallic, ceramic, and polymeric materials for military purposes. It was noted that surgeons began using these inert, durable materials to replace injured parts of the body. Hence, materials such as silicones, polyurethanes, nylon, methacrylates, titanium, Teflon® and stainless steel, which had principally been created for the industry, were then utilized in clinical applications. In 1930–1931, the team of physicians developed the pacemaker that could be taken around. In 1949, Dale Wurster became the first to unveil the Wurster process that enabled drugs to be encapsulated and then slowly released. The concept of modern controlled release through wrapped isoproterenol silicone tubes was introduced by Judah Folkman in 1964, and he later illustrated this when placing them in the hearts of animals [8].

Living organisms are capable of generating an array of polymers as a vital component of their morphology, cellular, and dry matter. The life cycle of an organism depends on biopolymers, which support essential cellular and metabolic functions. A schematic is presented in Fig. 1. Biopolymers are generated within the cytoplasm, organelles, the cytoplasmic membrane, cell wall components, and even extracellularly by enzymatic processes. Many biopolymers can be extracted from organisms such as plants and algae, which are primarily found in organic habitats. For instance, nutrient agar and alginin can be derived from red algae of the genus *Gelidium* or various brown algae commonly known as seaweeds [1]. Some biopolymers can also be synthesized through in vitro reactions utilizing purified enzymes in cell-free systems. In the case of polymerase chain reaction (PCR) heat heat-resistant DNA polymerases synthesize defined, monodisperse DNA molecules. Biopolymers, e.g., starch, dextran, can be produced through fermentation processes in many industrial processes. Biopolymers produced biologically can happen intracellularly, or they can be produced extracellularly, creating complications for downstream processing of biopolymers in purified forms [9].

Many different types of polymers may be synthesized by living material, and in most living things, biopolymers are often the predominant component of cellular dry matter. Most biopolymers are essential for the cells, and their functions are as diverse and complex as their structure. The biopolymers perform a variety of essential functions for an organism, which might include –

- Expression and conservation of genetic information.
- Reaction catalysis, energy or carbon storage, and other beneficial nutrient storage.
- The ability to sense biotic and environmental cues and defensive abilities against other cells and harmful environmental substances.
- Interaction with other living things and the environment.
- Mediating adherence to the surface (not strictly attaching) of other organisms or non-living matter, etc.

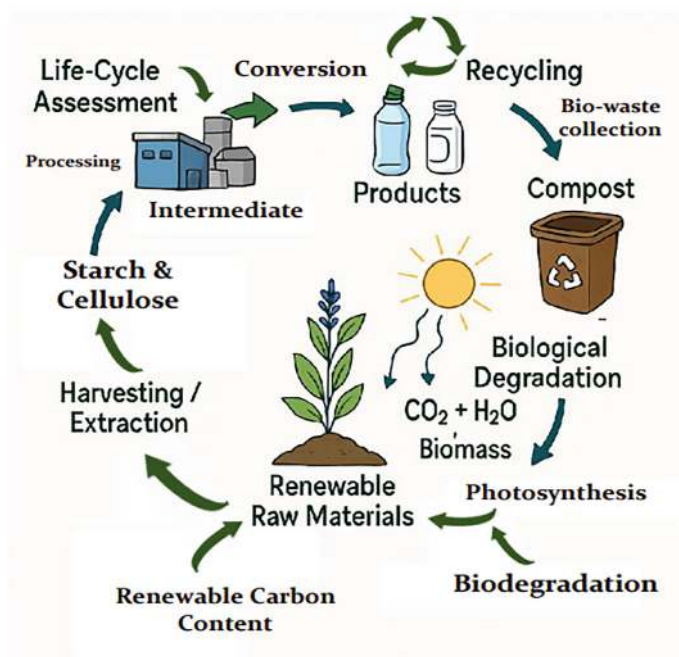


Fig. 1 A graphical abstract provides an overview of the importance of biomaterials produced or degraded naturally, their classification, and their applications [5]

All biopolymers are produced by enzymatic reactions in the cytoplasm and in several cell compartments or organelles, at the cytoplasmic membrane along with cell wall structures, upon the outside of cells or even on their surface, and in different parts of a cell depending on the type; that is, depending on the type, biopolymer formation may start in one area of the cell and proceed in another [9] (Fig. 2).

3 Classification of Biopolymers

The main classification criteria for biopolymers are outlined below: biopolymers can be categorized as either biodegradable or non-biodegradable based on their biodegradability; biopolymers can be categorized as either originating from fossil fuels or renewable natural resources, in addition to being categorized as elastomers, thermoplastics, or thermosets depending on how they respond to temperature, biopolymers can also be categorized as blends, laminates, or composites based on their composition [10]. A great variety of both natural and synthetic biomaterials, biodegradable and non-biodegradable, have been studied as drug delivery systems for health caregiving and tissue engineering purposes. For example, bioceramics, great biocompatible and composite polymers, and hydrogels have been studied and

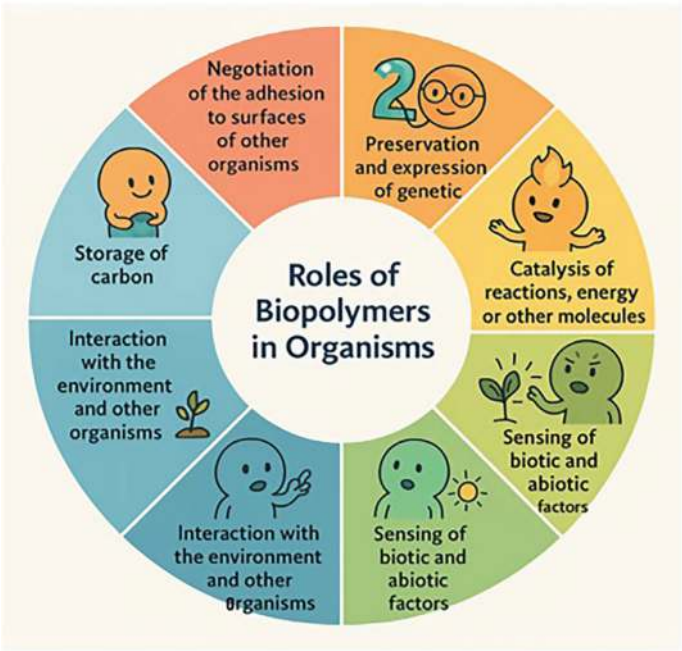


Fig. 2 Biological role of biopolymers in living organisms [9]

investigated [6]. Other than this, several biopolymers have been created for use in industrial plastic, absorbents, biosensors, food additives, packaging, textiles, water treatment chemicals, and data storage [11] (Fig. 3).

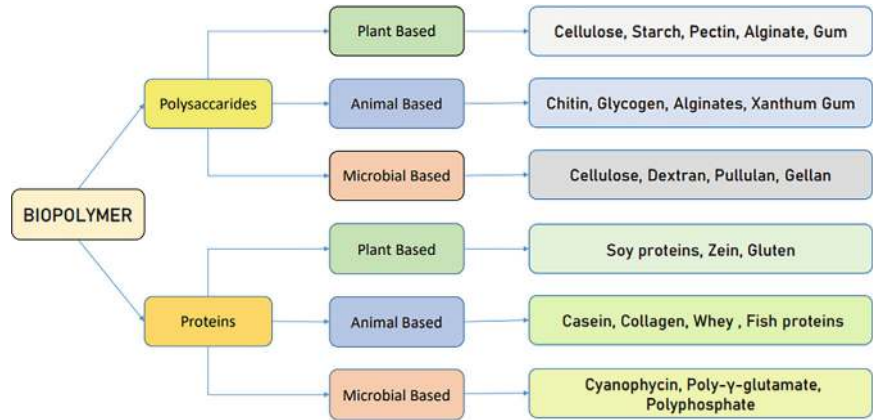


Fig. 3 Classification of biopolymers based on their sources [12]

Depending upon the origin of the raw material biopolymers can be segmented into three main categories, which are:

(I) Natural, (II) Synthetic, and (III) Microorganism-based biopolymers [6]

Natural resource biopolymers can come from microorganisms, plant sources, and animal tissues, and can even be synthesized from air, land, and sea living organisms. For example, microorganisms like bacteria, fungi, yeasts, molds, smuts, and other forms of what can be classified as primitive life forms can also produce an incredible range of polymeric biomolecules with prominent structural and biochemical properties. These biomolecules are often classified as either proteins or polysaccharides. Plants have been a valuable and renewable source of polysaccharides and proteins for thousands of years, and animals can also provide these valuable natural structures to biomaterials, regardless of how developed they may or may not be living on land, water or air; whether in the developed or undeveloped forms capable of providing biomaterial with significant potential in the biomedical arena. Apart from deoxyribonucleic acid (DNA), which is the genetic material present in all living organisms, examples of such arrangements include proteins (such as collagen, elastin, and gelatin), glycosaminoglycans (such as chitin and hyaluronate), and proteoglycans [13].

Based on the monomeric units that are utilized and, consequently, the resulting biopolymer structure, biopolymers may be divided into three broad categories:

- (i) **Polynucleotides (RNA and DNA)**—long polymers with 13 or more nucleotide monomers.
- (ii) **Polypeptides**—short polymers with amino acids.
- (iii) **Polysaccharides**—linear bonded polymeric carbohydrate structures.

Due to their flexible, elastic, and gel-like qualities, materials made from these molecules fall in between liquids and solids. Because the structures are continuously changed by enzymes over the life of the organism, biopolymers are intelligent and sensitive materials found in living things. Environmental changes continually modify biopolymers [7].

Numerous sequences can be found in the general biological substance known as nucleic acid. These polymers are made up of monomer units called nucleotides. Nucleic acids are linear polymers of one or more nucleotides composed of this smaller molecule (the monomer unit), such as DNA and RNA. Numerous molecules in sequence make up the general biological material known as the nucleic acid [14]. The covalent peptide bond that connects amino acids allows polypeptide molecules to unite to form proteins. A residue is an amino acid that is a member of a linked chain of a protein, and the protein backbone is the chain nitrogen, oxygen, and carbon (Fig. 4) [15]. Three amino acids that have undergone peptide bonding combine to form the polypeptide, as shown in the figure [13].

Synthetic polymers generated from biomass include polylactic acid (PLA), whereas petroleum-derived polymers include polyethylene, polyamides, polystyrene, polyglutamic acid (PGA), polyvinyl alcohol (PVA), and polycaprolactone (PCL). Biopolymers derived from microorganisms include bacterial

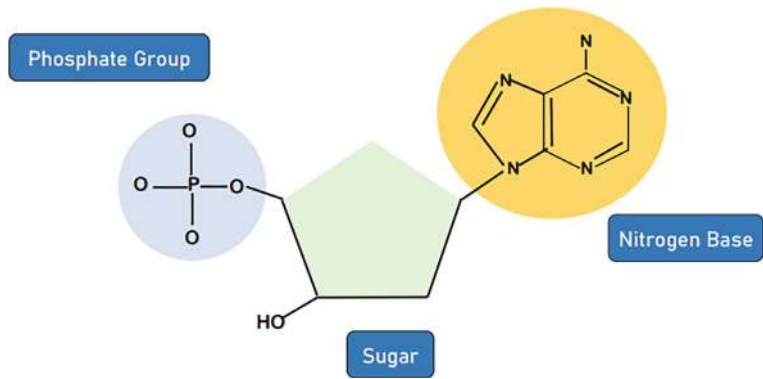


Fig. 4 A nucleotide monomer showing phosphate, sugar and nitrogenous base group [15]

cellulose, levan, curdlan, gellan, dextran, polyhydroxy alkanooates (PHAs), polyhydroxy butyrate (PHB), and poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV). However, the metabolism of microbial polysaccharides cannot be ignored, leading to the synthesis of bio-active polymers such as xanthan, capsular polysaccharides, and exopolysaccharides. Applications for these polymeric substrates include packaging, agro-industrial, pharmaceutical, agricultural, and environmental [16, 17] (Table 1).

Table 1 Classification of biopolymers

Classification	Origin	Biopolymers	References
Plysaccharides	Plant/algal	Starch (amylose/amylopectin), Cellulose, Agar, Alginate, Carrangeenan, Pectin, Konjac, Various gums (e.g., guar)	[11]
	Animal	Chitin/chitosan, Hyaluronic acid	
	Bacterial	Xanthan, Dextran, Gellan, Levan, CurdIlan, Polygalactosamine Cellulose (bacterial)	
	Fungal	Pullulan, Elsinan, Yeast glucans	
	Lipids/surfactants	Acetoglycerides, waxer, surfactants, Emulsan	
Proteins		Silks, Collagen/gelatina, Elastin, Resilin, Adhesives, Polyamino acids, Soy, zein, wheat gluten, casein, Serum albumin	
Polyesters		Polyhydroxyalkanoates, Polylactic acid	
Specialty polymers		Shellac, Poly-gamma-glutamic acid, Natural rubber, Symthetic polymers from natural fats and fats and oils, nylon from castor oil	

3.1 *Biobased Polymers Directly Extracted from Biomass*

Renewable resources that are rich in proteins, polysaccharides, lipids, and other nutrients include wood, agricultural waste, plants with natural fibers, grasses, and synthetic fibers [18]. Biopolymers are mostly categorized based on the source material. Since polysaccharides make up the majority of terrestrial biomass and are the most abundant renewable material in the world, they are among the most well-known forms of biopolymers. They have structural roles in the skeletons of animals (chitin) and some plants (cellulose, pectin). Other polysaccharides may also function as energy storage units (e.g., starch and glycogen) [19]. Polysaccharides are long linear or branched chains of monosaccharide units (as seen with cellulose) linked by glycosidic linkages, but upon hydrolysis can be converted to monosaccharides or oligosaccharides by the hydrolytic reaction. Some of the major classes of polysaccharides to note would be the storage polysaccharides (starch and glycogen) and structural polysaccharides (cellulose and chitin) [15]. Each of these polysaccharides has a unique molecular structure that varies according to the source, the plant component or organism, and the extraction technique. In several uses, polysaccharides are completely biodegradable, biocompatible, a renewable resource, and CO₂-neutrals [20]. Due to these properties, polysaccharide-derived polymers are used in a variety of applications, including bioplastics, food packaging, and tissue engineering [21].

Cellulose is the primary building block of all plant cell walls; it is frequently referred to as the most common biopolymer and world-wide molecule. This polysaccharide, which is found in natural fibers, is composed of glucose units that repeat. Humans cannot digest it, and it is insoluble in water [19]. Hemicelluloses, another important biopolymer and a major constituent of plant cells, act as a matrix for cellulose microfibrils that resembles cement. Twenty to thirty percent of dry plant biomass is made up of hemicelluloses. Pectin is also found in plants' main cell walls, where it serves as a structural polysaccharide at every stage of development. Alginate is another biopolymer generated from seaweed that is present in cell walls and adds strength and flexibility [22]. Amylose and amylopectin are two polysaccharides that combine to form starch, a semi-crystalline macromolecule [23].

Mushroom cell walls and arthropod epidermis include **chitin**, a material originating from plants and animals [13, 17]. Many chitinases, which are extensively dispersed in nature and may be found in bacteria, fungi, plants, and the digestive tracts of most animals, make chitin in the gastrointestinal system of mammals inert and biodegradable [20]. However, the primary result of chitin deacetylation, the biopolymer chitosan, has generated attention in the fields of food, agriculture, biomedicine, and pharmaceuticals [24–29].

One of the primary categories of renewable biopolymers are protein derivatives, which are chains of amino acids connected by peptide bonds [30, 31]. Among other functions in living organisms, proteins are necessary for immunological response, cell adhesion, and cell signaling [15]. Plant proteins such as soybean, wheat, cottonseed, maize zein, and soy protein can be utilized to make biobased polymers. Blood meal, gelatin, collagen, keratin, gluten, egg protein, whey protein, and gelatin are

examples of animal proteins that can be utilized as raw materials [30, 31]. These byproducts can also be fermented or deproteinated to create protein-based biopolymers [20, 30, 31]. Certain beneficial properties of protein-based biopolymers, such as their high heat resistance, water resistance, biodegradability, and biocompatibility, may make them appropriate for application in the packaging industry in the future [32].

One theory is that gluten is a byproduct of digesting wheat flour starch grains. Even though wheat proteins are typically thought of as storage proteins, gluten has unique viscoelastic qualities that are uncommon elsewhere and should be taken into account when using it in structural forms such film production. Collagen is a biomaterial with potential interesting properties which include plenty of availability, biodegradable, non-toxic, biocompatible, high tensile strength, and low extensibility [20]. Collagen is highly applied in food and cosmetics industries [32]. Gelatin is a useful water-soluble protein that is produced by hydrolyzing animal waste with acid or alkali. The main sources of gelatin are tendons, bones, and animal hides. In addition to its intriguing viscoelastic properties, gelatin is being used more and more as a thickening, stabilizing, or gelling ingredient. Gelatin can produce gels and films and is readily accessible, inexpensive, and biodegradable [20].

Hydrogels have gained popularity in biomedical applications recently because to their special properties, which include an elevated water content, softness, versatility, and biocompatibility. Hydrogels are also utilized in medication delivery systems and tissue engineering due to the previously described properties [33]. Hydrogels must be cross-linked in order to improve them, stop deterioration, and create appropriate hydrogels for in vitro and in vivo applications [34]. For example, cross-linked hydrogels are hydrogels of gelatin that have been cross-linked with dextran dialdehyde; these hydrogels have a greater storage modulus than cross-linked gels [33].

Biopolyesters are a type of polymers that come from different microorganisms and plants. They are materials that have the desired qualities of plastics without necessarily being bad for the environment [35, 36]. In their chains, there are functional groupings. Materials that are biodegradable, renewable, and bio-assimilable are produced when biopolyesters are polymerized. While this depends on the kind of biopolyester, polyesters are often water-resistant [10]. Polycaprolactone (PCL), polylactic acid (PLA), and polyhydroxyalcanoates (PHAs) are well-known natural polyesters [37]. PLA is an eco-friendly polyester derived from renewable resources, including fermented sugarcane, cassava as well and maize starch. Microorganisms in nature that break down PLA are common. PLA is biodegradable once it duplicates polymerization [37, 38].

Most often used applications are in the food and pharmaceutical sectors [37, 38]. PHAs may be created by a range of bacteria and are the only aliphatic polyesters that are entirely made by microorganisms [20]. Majority of these bacteria are found in harsh settings like the high seas and activated sludge. Because of their physiochemical, biodegradable, and biocompatible qualities, which enable effective drug administration, they are often employed in the biomedical industry. Another subclass

of polyesters is called polycaprolactone (PCL), which is made by catalytically polymerizing caprolactone. PCL degrades more slowly, is less permeable to water, is more hydrophobic, and is highly permeable [37].

4 Role of Biopolymer in Biomedical Sciences

Biopolymers have multiple functions in the human body such as encapsulating cells which enables the forming of tissues and controlling their behavior by sending signals. Moreover, they moderate skin hydration and elasticity to aid in maintaining equilibrium. They provide flexibility to joints and the gastrointestinal tract utilizing lubrication while guarding against pathogens by accumulating into the protective mucus gel that coats the human eyes and the respiratory tract [7]. Also, biopolymer scaffolds accomplish numerous tasks including transporting signals that monitor cell activities and regulating skin hydration, elasticity, and pathogen defense while providing flexibility to joints through lubrication. This section covers the promising application areas of biopolymers and their composites along with the challenges, state-of-the-art methods, and innovation in the carriers [15].

Biodegradable products have specific importance in medicine. They can be sub-classified into five categories as the scope of each encompasses a broad area within medicine:

- Drug Delivery systems.
- Surgical wound closures.
- Healing devices and surgical implants products.
- Bioresorbable scaffolds used in tissue engineering.
- Biosensors and other diagnostic applications.

4.1 *Drug Delivery Systems*

Effective conjugation of a therapeutic agent and a drug delivery vehicle allows for the easy release of an effective therapeutic agent in a predetermined dosage, which is one of the basic characteristics of any drug delivery system [39, 40]. The drug attachment delivery agent will always depend on the formulation of the drug molecules, regardless of whether they are hydrophilic or hydrophobic [15]. The most sensible drug delivery agent design would ensure that these medications are linked together efficiently. Furthermore, the drug's carrier would stop a therapeutic substance from being broken down by enzymes before its regulated release. The carrier would guarantee biodegradation, non-toxicity, and—most importantly—that the discharge would not harm the body after delivery [39, 41].

The ability of polymeric materials to facilitate the efficient and multifunctional delivery of pharmaceuticals is made possible by the novel properties of biopolymers and their derivatives, which include water solubility, non-toxicity, biodegradability, biocompatibility, and ease of modification [11]. Above all, by regulating the drug's release, these biopolymers will reduce its adverse effects. Three groups of commonly used biopolymers are polysaccharides, polypeptides, and proteins used as drug delivery systems [15]. One of the main benefits of polysaccharide molecules is their ability to control the entire drug delivery system. Therapeutic drugs are dispersed or encapsulated in biopolymer matrix through encapsulation or the formation of micro/nanoparticles, liposomes or hydrogel formation, polymer-drug conjugation, and micelles [42, 43].

Chitosan: Chitosan (CH) is a cationic polysaccharide with extensive applications in various drug delivery systems, produced by the N-deacetylation of chitin [44–46]. Currently, CH is effectively applicable via oral, vaginal, nasal, parenteral, and injectable routes. CH must therefore lessen enzymatic degradation since it can merge with biological tissue. Additional benefits of chitosan-based drug delivery systems include the medication's stability and absorption within the polymer matrix. One of the most effective drug delivery techniques was achieved by conjugating chitosan with varying molecular weights; the cleavage conditions varied according to the kind of medication and were sensitive to glutathione (GSH) or pH [15]. The formation of hydrogels with chitosan also accommodates other sensitive proteins or genes intended for delivery [47].

Cellulose: The most widely available biopolymer is cellulose, which has superb mechanical and biological properties including biocompatibility, biodegradability, and low cytotoxicity [48]. For drug delivery systems, cellulose with varying aspect ratios, including bacterial nanocellulose (BNC), cellulose nanomaterials (CNC and CNF), and microcrystalline cellulose (MCC), are among the most promising materials [49–51]. BNC is commonly modified by etherification, esterification, phosphorylation, or amidation to incorporate any diffusion barrier, which drastically changes the rate of drug release [52–54].

Collagen: Collagen is a highly plentiful protein from animal sources containing a triple helix framework of an amino acid repeat unit of glycine–proline–hydroxyproline. Due to its remarkable biocompatibility, collagen has been used in drug delivery techniques as hydrogels, films, coatings, or microparticles [55]. From small-molecule drugs to biomacromolecules (DNA, proteins, or even cells), collagen with a binding protein and denatured collagen (gelatin) have both been used to deliver a range of therapeutic agents. Contact lenses sold under the name BioCora collagen shields may be used to treat bacterial keratitis, HSV keratitis, amphotericin-B, vancomycin, pilocarpine, gentamicin, and other corticosteroids and water-conjunctival antibiotics [15, 56].

4.2 Tissue Engineering and Regenerative Medicine

Tissue engineering is the most promising technique for using biopolymer composite implants to repair and regenerate biological tissues. Biopolymer composite scaffolding must mainly replicate the collagen-rich extracellular matrix (ECM), which supports collagen structurally and biochemically, to provide the best supporting framework for tissue in tissue engineering and regenerative medicine. The traditional cell culture method is employed to produce recombinant tissue that is as similar to nature as feasible. This technique uses the biochemical and physical characteristics of natural tissues *in vivo* to promote the development or replication of the recombinant tissue. In scaffolding, this is done by recomposing the original ECM structure and using scaffolds with similar surface topography [15, 57].

The assembly of new biopolymer scaffolds is a particularly critical element of regenerative medicine. Even though these biopolymers have desirable properties as scaffold tissue materials, they may be combined using a variety of assembly methods to provide a wide range of useful scaffolds for diverse tissues. Three fundamental techniques for creating biopolymer scaffolds are three-dimensional (3D) printing of scaffolds [58], electrospinning of fiber scaffolds, and assembling into bulk hydrogel scaffolds [57]. Since each assembly technique has unique advantages for scaffold formation, scaffolds are increasingly being designed to use a variety of assembly techniques and biopolymer classes to replicate natural extracellular matrix [57] (Fig. 5).

Hard Tissue Scaffolds

Due to a substantial increase in people suffering from deficiencies, especially in hard tissue, there is a demand in numerous medical applications such as bone fractures and cartilage [59, 60] defects [61], joint replacements [62], bone plates, and

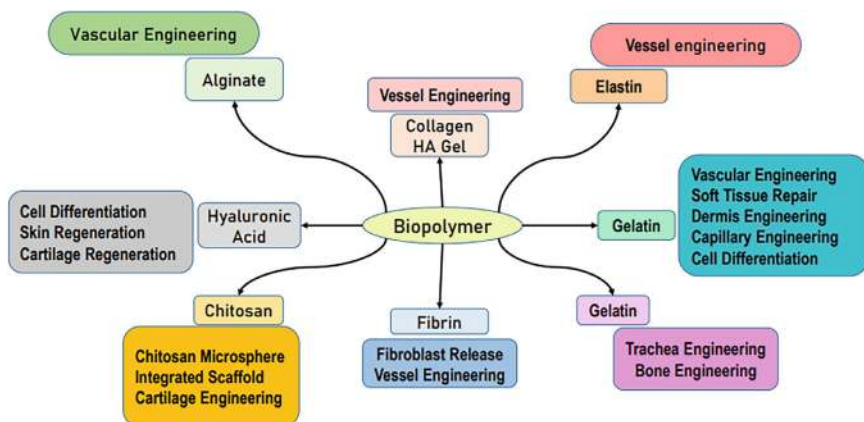


Fig. 5 Function of diverse biopolymer composites in tissue engineering and as scaffolds for different organs [16]

bone cement [63]. Currently, biomaterials and their derivatives (mainly proteins and polysaccharides) are combined with microcrystalline hydroxyapatite, resulting in a biofunctional composite material, which is designed to restore the functional biomechanical function of neo-formed tissues (including appropriate biomineralization) [15].

The most abundant, most prominent and integral physical protein of vertebrate ECM, collagen, is deemed a large protein in triple-helical arrangement and forms one of the smaller complexes in the native construct and tabulated skeletons to tissue scaffolds in mammals. Collagen-based composites for bone tissue regeneration have been the subject of several recent investigations and applications [64]. Apart from collagen, additional biopolymers that are used as natural polymers with hydroxyapatite filler include chitosan, silk fibroin, alginate, starch, cellulose produced by bacteria [65], and cross-linked cellulose nanocrystal (CNC) aerogels [66]. However, because the primary issue with biopolymer structures is their poor mechanical responsiveness, Hydroxyapatite (HAP) is the sole factor that might impede the bioregeneration process. Another improved biopolymer composite can be used to repair this and restore the bone tissue [67, 68].

Soft Tissue Scaffolds

The second type of biological tissue replacement concerns scaffolds made of soft tissues. With a stiffness of 0.1–1 kPa for brain regions and 230 kPa for the spinal cord, nerve tissues are primarily referred to be soft tissues [15]. Together with the related bodily parts, it consists of muscles, nerves, and other tissues ligaments, tendons, skin, blood vessels, lungs, cartilage, intervertebral disks, fat, etc. [69]. Diseases, aging, genetic flaws, or trauma can all harm these tissues, leading to dysfunction, deformity, or even death. To promote cell development and tissue regeneration in the application region, scaffold structural characteristics and composition should be tailored to the host's natural extracellular matrix system [70, 71].

As shown in Table 2, the remarkable properties of collagen, a naturally occurring polymer, make it a strong candidate for use in soft tissue engineering applications. Collagen is the most basic kind of extracellular matrix present in stiff, semi-rigid, and soft connective tissues. It is essential to create and embrace a 3D architecture. Moreover, it establishes a framework for tissue growth. Two popular in vitro techniques for creating collagen hydrogels are chemical and physical cross-linking [72].

As a naturally occurring polymer, gelatin is less antigenic than the native collagen, as it is sourced from degraded collagen. Other structures with greater stability and likely cell adherence can be formed with this gelatin [80]. The capacity of cells to survive, differentiate, and proliferate into the cell types listed in Table 3 makes gelatin-based scaffolds appealing for utilization in tissue engineering [15].

Elastin is a protein that has a physiological role in the majority of elastic tissue, including blood vessels, ligaments, tendons, muscles, skin, and lungs. For tissue engineering applications, elastin should have structural stability, bioactivity, and biocompatibility in addition to its elastic qualities [86]. Because of their favorable qualities, such as their easy availability, biodegradability, non-toxicity, amphiphilia, antibacterial activity, and favorable morphological and structural traits, plant proteins

Table 2 List of the recently reported collagen-based scaffolds

Materials	Fabrication techniques	Area of applications	References
Collagen/poly (3- acid)/hydroxybutyric gelatin	Electrospinning	Skin tissue (wound healing)	[73]
Collagen/chitosan	Freeze drying, dehydrothermal treatment	Skin tissue	[74]
Collagen hydrogel	3D printing	Cartilage tissue	[75]
Collagen/elastin hybrid	Excimer-laser ablation	Skin tissue	[76]
Collagen gel	Molding technique	Vascular tissue	[77]
Collagen/alginate/fibrin	Solution polymerization	Soft tissue	[78]
Collagen/silk fibroin	Cross-linking	Corneal tissue	[79]

Table 3 List of the recently reported gelatin-based scaffolds

Materials	Fabrication techniques	Area of applications	References
Gelatin/PEG	Cryogelatin	Soft tissue (neural, cardiac and skin)	[81]
Gelatin/PU	Electrospinning	Soft tissue	[82]
Gelatin methacrylamide (GelMA)/poly(ethylene glycol) (PEG)	Thiol-yne coupling	Soft tissue	[83]
Gelatin-chitosan	Electrospray ionization	Injectable tissue engineering scaffolds	[84]
Gelatin/poly (glycerol-dodecanedioate) (PGD)	Glectrospinning	Soft tissue	[85]
Gelatin/PCL	Glectrospinning	Vascular tissue	[70]
Tecophilic/gelatin	Glectrospinning	Blood vessel tissue	[71]

are excellent candidates for soft tissue scaffold precursors. Poly (glycerol sebacate) (PGS) was combined with the plant protein zein by Vogt et al. to create soft tissue scaffolds for the regeneration or restoration of cardiovascular tissue [87]. Another kind of regenerated cellulose, carboxymethyl cellulose (CMC), might be an excellent choice for a biomaterial. The very desired chemical characteristics of CMC are displayed in Table 4.

Deacetylated from chitin, chitosan is one of the most well-known biomass polysaccharides with high adsorption, biodegradability, non-toxicity, and biocompatibility properties. As Table 5 [15] shows, there are several advantages to using chitosan-based scaffolds, including in tissue engineering, drug delivery, biomedical applications, etc. Researchers mixed chitosan-based scaffolds with other natural or synthetic polymers reported in the literature in an attempt to promote them [95]. One of the most popular synthetic polymers in biomedicine is polyurethane because of

Table 4 An overview of various recently published scaffolds made of alginate

Materials	Fabrication techniques	Area of applications	References
Alginate/collagen (Type I/ TypeII)	Freeze drying	Cartilage tissue	[88]
Alginate and gelatin	Cross-linking	Soft tissue	[89]
Alginate/O-carboxymethyl chitosan/nano fibrin	Ionic cross-linking	Adipose tissue	[90]
Alginate nanobeads/fibrin	Double syringe apparatus	Soft tissue	[91]
Alginate foam	Freeze drying	Soft tissue	[92]
Polypyrrole/ Alginate	Ionic cross-linking	Neural tissue	[93]
Alginate/gelatin	Cross-linking	Wound Healing	[94]

Table 5 List of the recently reported chitosan-based scaffolds

Materials	Fabrication techniques	Area of applications	References
Chitosan/keratin/gelatin	Freeze drying	Soft tissue	[96]
Chitosan/hyaluronan	Metal-free click chemistry	Soft tissue	[97]
Chitosan-poly(ϵ -caprolactone) dialdehyde	Cross-linking	Soft tissue	[98]
Agarose-chitosan coated silver nanoparticle	Cross-linking	Soft tissue	[99]
Chitosan/PVA/methylcellulose	Freeze drying	Soft tissue	[100]
Chitosan nanofibrous mats	Electrospinning	Soft tissue regeneration	[15]
Chitosan/methacrylated silk fibroin	Photopolymerization	Cartilage tissue	[101]

its remarkable biocompatibility and robust mechanical and physical characteristics [15].

4.3 Wound Healing and Antimicrobial Applications

The skin, the biggest organ in vertebrates, serves as the body's main line of defense against damaging situations, including infection, pollution, and the impacts of harsh environmental conditions. Skin has a vital role in fluid homeostasis, thermoregulation, sensory detection, and self-healing properties in addition to its defensive role. The acellular dermis, which is mostly made up of collagen and extracellular matrix (ECM), make up the skin's three primary layers, which contributes to the mechanical

strength and pliability that the skin requires and supports bundles of nerves, vasculature, and lymphatics [15]; the hypodermis, which is the innermost layer, which has fat tissues that serve to provide thermal insulation and mechanical protection from external insults [102]. The number of layers engaged and the skin regions that have been wounded are further criteria for classifying wounds. It is divided into the three most prevalent forms based on this characteristic [15].

The three layers of skin provide protection, but a variety of factors, including trauma, blood flow, burns, and aging, can cause harm to the skin. Wounds can be defined as any damage or injury that interferes with the skin's natural function and anatomic structure [15]. While more severe wounds may require further care to heal, mild wounds can heal on their own without any additional care. When significant wounds are treated further, the skin's integrity will be preserved; if major wounds are not treated further, the skin's integrity will be lost, and there may be substantial consequences that could cause morbidity and death [103] (Fig. 6).

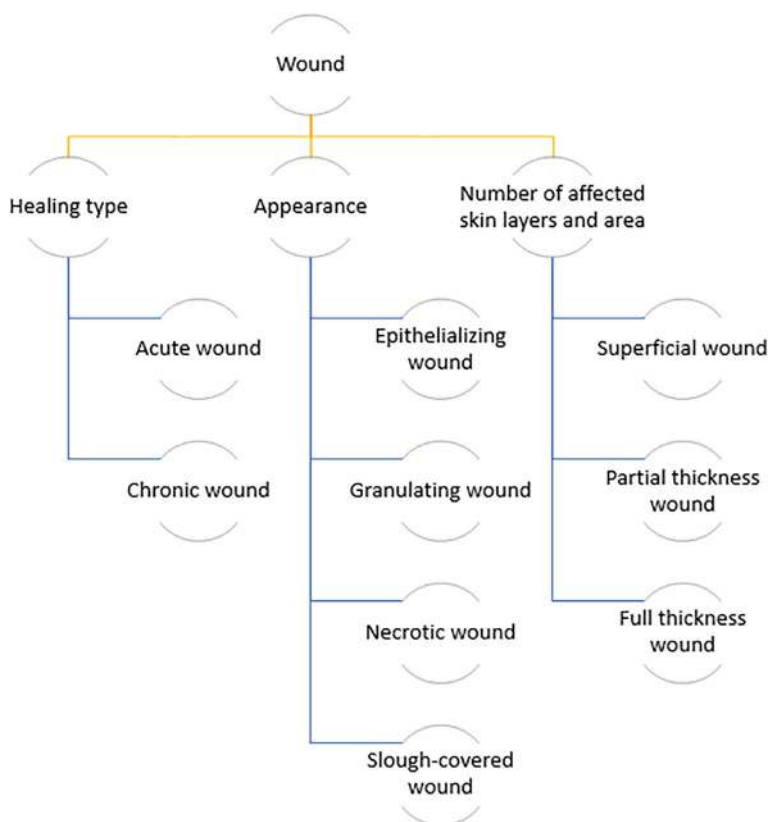


Fig. 6 Three major categories exist for wounds, and within those categories are several subtypes of wounds [15]

Classification of Wounds

Acute wounds and chronic wounds are two main types (i.e., based on time to heal) of wounds, and time to heal is a crucial factor in wound and injury care [15]. Acute injury is characterized by subcutaneous impairment due to damage to the superficial dermis or epidermis [104]. While heat damage, surgical incisions, abrasions, and lacerations are the main causes of acute wounds, chronic wounds are more likely to reoccur and are linked to certain disease processes (such as diabetes or tumors). Acute wounds heal in around 8–12 weeks, whereas chronic wounds often require more than 12 weeks. Depending on how the damage looks, we may classify wounds in four different ways, in addition to the healing process and recovery duration.

Concept of Wound Healing

The healing of wounds is vital to life. The process of healing a wound involves moving from the site of harm to the repaired tissue. The entire healing process, however, may be broken down into phases for understanding purposes. When many immunologic and biologic systems work together, it is essential for wound healing to be effective. At each stage of the healing process, various cell types in the wound bed coordinate in a well-defined, step-by-step controlled process [15]. These incidents may be roughly categorized into four successive incidents;

- (1) **Coagulation and hemostasis**, which initiates immediately after any injury;
- (2) **Inflammation**, which immediately follows;
- (3) **Proliferation**, which occurs on day three post-injury and encompasses the more significant healing processes; and finally,
- (4) **Wound remodeling**, development of scar tissue. The period for wound remodeling can last as long as one year or more.

The coagulation and hemostasis mainly deter exsanguination. When exsanguination is deterred, the vascular system is protected, maintaining the function of vital organs, regardless of an injury. After hemostasis, inflammatory activities occur almost 24 h after the injury occurs. Inflammation creates a resistant barrier against invading microorganisms. The entire inflammatory phase consists of two phases: early and late inflammatory phases. On the third day after the damage, the proliferation begins and continues for the following two weeks. The epithelium covers the wound, and new granulating tissues develop. Blood vessels, fibroblasts, and microphages all arrive at the wound bed at the same time and function as a cohesive team. The creation of scar tissue and new epithelium is also a result of the remodeling phase. It might take one to two years for scar tissue to form [15].

According to the source, the following three types of frequently used wound dressing materials are classified [105]: **(I) biologic, (II) synthetic, and (III) biologic-synthetic composite**. Each kind of dressing material is designed and utilized for its specific properties, which is the reason why these materials, or sealants, are used/put on specific types of wounds. Regardless of their use or classification, all dressing materials need to possess specific attributes, like maintaining the right amount of moisture with exudate encompassing the wound bed, encouraging gas exchange,

effectively eliminating excess exudate while simultaneously serving as an inhibitor to microorganisms, being easily accessible with low processing time and expense, possessing antimicrobial activity, providing thermal insulation, accelerating wound healing, and stimulating growth factors [102, 105].

Biopolymers in Wound Healing

Biopolymers and natural polymers are the most promising options for wound and burn healing. Wounds and burn injuries have long been treated with natural polymers because they are biocompatible, biodegradable, and similar to extracellular matrix (ECM) [106]. These organic healing agents are mostly found in living organisms, including fungi (chitin), algae (alginate), bacteria (bacterial cellulose, exopolysaccharides), plants (cellulose, starch, and natural rubber), and mammals (collagen, hyaluronic acid, and chitosan) [107].

One of the fundamental structural proteins of all organs, **collagen** is mostly found in connective tissues. The ECM and collagen have comparable structural and functional traits, which further influenced the rationale to apply collagen matrices in wound healing purposes. Chemically, collagen is a triple helix fibril consisting of a repeating amino acid polymer that is bonded with peptide linkages. Collagen has a crucial role in natural healing from the induction of clotting to the formation and maturity of the final scar [15]. Formulations for natural or biocollagen dressings come from avian, bovine, and porcine sources [108]. Numerous types and biological applications of collagen have been documented in the literature; Table 6 lists a few of these.

Table 6 Applications of collagen in wound healing

Application	Material	Formation	References
Wound dressing	Thermostable and biodegradable fibril	Collagen–alginic acid cross-linking	[109]
Skin diseases, anti-oxidant, severe burns	Collagen- α -tocopherulate biopolymer	Solid-phase synthesis	[110]
Artificial vascular grafts and wound repair	Nanofibrous collagen scaffolds	Electrospinning	[111]
Skin grafting	Microfiber scaffold	Collagen seeded with human fibroblasts and keratinocytes	[112]
Cutaneous wound infections	Hydrogels	Type I collagen and minocycline hydrogel were prepared by response surface methodology and Taguchi's approach	[113]
Deep skin wounds	Sponges	Chemically reaction of hexamethyldiisocyanat with collagen	[15]

Chitin is the biopolymer that is utilized in wound healing the second most frequently [15]. Inert polysaccharide copolymers called chitins are frequently found in invertebrates, including green algae cell walls, crab shells, insect cuticles, mushroom detritus, and yeasts. Chitosan is a chitin derivative that is mostly deacetylated and active. They are excellent choices for wound healing since they are non-toxic, biocompatible, biodegradable, antimicrobial, and hydrating—especially for open and serious wounds. The hemostatic activity of fibroblasts supports the growth of their layer throughout the healing process [101].

As polymer generated from plants, cellulose has several uses in the treatment of wounds. A repeating unit of β -d-glucose joined by β -1, 4-glycosidic bonds forms the cellulose molecule. High purity, tensile strength, high exudate holding capacity, biodegradability, and a distinct nanofibril morphological network structures are just a few examples of the cellulose film's excellence. qualities. [101] Because cellulose retains a lot of water, it keeps the wound moist, and wet wounds heal more quickly because the repairing tissue is constantly receiving growth factors and other nutrients [15].

Antimicrobial Activity

Since chitosan derivatives may be engineered to have higher bacteriostatic activity than chitosan, they offer intriguing qualities that make them suitable for biomedical applications. When grafted onto chitosan, ethylene diamine tetraacetic acid (EDTA) enhances its antibacterial qualities by chelating magnesium, which typically stabilizes gram-negative bacteria's outer membrane. Since carboxymethyl chitosan either adsorbs onto the negatively charged bacterial surface and breaks the cell membrane or prevents bacteria from accessing necessary transition metal ions, it has also been seen to boost chitosan's antibacterial action. Chitosan grafted with EDTA as a hydro-alcoholic gel component intended for topical administration and carboxymethyl chitosan for periodontal pocket reduction in dentistry are examples of materials that have been used in wound healing systems. Membranes grafted with chitosan and chitooligosaccharide shown antibacterial efficacy against *Escherichia coli*, *Pseudomonas aeruginosa*, and methicillin-resistant *Staphylococcus aureus* (MRSA) [114].

4.4 Biosensors and Diagnostic Applications

In general, the research of novel electrochemical biosensor designs for medical monitoring has been improved by high-tech [15]. The most researched polysaccharides used in this situation are chitosan and carboxymethyl cellulose [115, 116]. Their notable characteristics include biodegradability, biocompatibility, non-toxicity, the capacity to create adherent thin films, renewability, and pervasiveness [117]. The benefits of biopolymer nanofibers, such as their antibacterial activity, potential use in drug delivery systems, implanted biomaterials, biosensors, and tissue engineering, have attracted particular interest recently [118].

5 Recent Advances and Miscellaneous Applications

Recently, it has been noted that smart polymeric materials can respond to major environmental changes with only minor adjustments. Other names for these polymers include environmentally sensitive polymers, stimuli-responsive polymers, and smart polymers. The microstructure of smart polymers can change quickly and reversibly according to tiny environmental cues. Temperature, pH, solvent or ionic content, electric field, light intensity, and certain ions are among the stimuli that have been shown to change the physical properties of polymers. Recent advancements indicate that the field is receiving exponentially more attention, and smart polymeric materials are being created for use in biotechnology and medicine [7].

Numerous kinds of smart biopolymers have been created for a range of applications. The following categories have been established for smart polymers based on the type of stimuli and how the polymer functions:

- i. **pH-sensitive smart polymers:** Smart polymers that are responsive to pH. This term refers to polymers that include ionizable functional groups that are sensitive to pH variations [7].
- ii. **Thermosensitive smart polymers:** These are temperature-sensitive smart polymers that react to changes in temperature by changing their microstructural properties. These are the most researched, used, and safe polymers for biomaterials and drug delivery systems [7].
- iii. **Stimuli-responsive smart polymers:** These include polymers that are sensitive to light, electricity, magnetic fields, and multiple stimuli [7].

In many medical applications, such as occlusion, suturing, covering, fixation, isolation, adhesion, cellular proliferation, controlled drug administration, contact inhibition, tissue guidance, etc., biopolymers are crucial (Table 7). The flexibility, strength, weight, and tear resistance of poly (L-lactic acid), poly (glycolic acid), and their copolymers, polyurethanes, are critical for grafting scaffolds supporting artificial blood vessels [119]. Polyesteramides have suitable mechanical and thermal properties that make them suitable for tissue engineering, hydrogel, and drug delivery applications. The majority of the hygiene and health-related products used in hospitals include disposable and non-disposable surgical masks, gloves, surgical gowns, towels, sanitary napkins, diapers, bed linens, surgical boots and caps, underwear shields, antimicrobial textiles, surgical drapes, wipes, etc.

Traditional surgical gown materials including cotton, polyester, and polyethylene can be replaced with biobased PET [120]. Additionally, polylactic acid is used to make hats, masks, and gowns [15]. Due to its extremely high absorbency, thermoplastic starch is also utilized in baby diapers [121]. The medical and sanitary sectors are the main users of several biomaterials, including collagen, chitosan, alginate fibers, catgut, and super absorbent polymers.

Table 7 Potential uses of biopolymers in the healthcare industry

S. No	Application	Polymer used	Possible biopolymer replacement	References
1	Suture	Poly(amide), poly(propylene), Poly (vinyliden fluoride)	PLA, PGA, PLGA	
2	Wound dressing	Poly (vinyl alcohol), cotton	PGA, PLA	
3	Tubing or blood bags	Poly (vinyl chloride)	PBAT, PHB	
4	Catheters	High-density polyethylene (PE), Poly (dimethylsiloxane), polyether ether ketone, poly (propylene)	PLA, PGA, PLGA, TPS, PCL	
5	Plasters	Toluene 3, 4 diisocyanate and polyethylene glycols (Lycra fibers)	PLA, TPS	[15, 122]
6	Surgical gowns	Cotton, polyesters, polypropylene (PP), PE	Bio-based (PET, PBT)	
7	Caps, masks, and gowns	Polyethylene terephthalate, cotton	PLA, TPS	
8	Surgical hosiery	PET, cotton, PP, PE	Bio-based PET	
9	Pillow cover	Polyesters	PLA, TPS	
10	Uniforms	Polyesters	Biobased PET, TPS, PLA	
11	Baby diapers	Polyacrylic acid, polyvinyl alcohol copolymers	TPS	

6 Future Perspective and Conclusion

Nature offers a diverse range of biopolymers that feature varying molecular structures and properties; these can be tailored through specific formulations and processing techniques. Recent advancements aimed at promoting sustainable energy solutions are concentrating on the development of eco-friendly materials. A significant focus has been placed on discovering and producing biopolymers along with their composite forms to replace synthetic plastics due to their remarkable characteristics. These materials have gained recognition for being biocompatible and biodegradable without toxins, positioning them as viable green alternatives in an expanding market.

After fabrication, the biopolymer and the biopolymer composites were structurally elucidated using characterization techniques, based on microscopy, spectroscopy, and diffraction. Biopolymers and biopolymer composites remained intact and useful as implanted devices in pharmaceutical and medical applications, gels, ointments, and wound dressing materials in wound healing, and scaffolds for tissues

and organs in tissue engineering. Right now, the market for biopolymer materials is expanding quickly in tandem with society's rising interest in sustainable development. Nonetheless, because the creation of biopolymer materials is costly, scientists are concentrating on creating less expensive biomass substrates in order to produce huge amounts of biopolymers at lower manufacturing costs. Improving the quality and performance of biopolymers to match those of synthetic polymers is the second major issue.

The incorporation of biomaterials into regenerative medicine formats has bettered the lives of millions of patients. Yet numerous challenges remain, leading to the necessity for more interdisciplinarity between the biomedical sciences, surgery and engineering. The fabrication of bionanocomposites is one promising route toward enhancing polymeric properties where the end polymer still possesses biodegradability. Although the subject of biomedical materials has gone far with the utilization of biopolymers, it will need extensive research to create a proper drug delivery system, which might be a better alternative method. Also, there is the need to realize how drug delivery systems function and how long it could take them to influence a tissue or cellular compartment regarding intention. These are difficulties in coming up with a solution for the existing unmet medical need. Since changes to the surface or chemistry can significantly alter the properties of cell-material interactions, there will likely need to be some extensive research into the surface and functionalization of biopolymers like nanocellulose. This could lead to a revolutionary advancement in biomedical materials. A wider view toward application of biopolymers in industries through incorporation of modifications or even blends of biopolymers with other ingredients would be a thrilling future for these biodegradable materials and their potential commercialization.

In conclusion, these biopolymers have contributed positively toward their delivery in applications, justifying further attention toward the abolishment of synthetic counterparts. This will open the door for the creation of more sophisticated smart biopolymers with controlled functional characteristics, with the process engaged in creating better biopolymers for biomedical purposes in mind.

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Chapter 2

Animal-Derived Biopolymers: Properties, Raw Material Sources, and Their Developmental Process

Zakir Md Hossain

Abstract Animal-derived biopolymers constitute a versatile group of materials that are naturally produced and have gained increasing attention for their remarkable biodegradability, biocompatibility, and sustainable nature. These polymers, including chitin, chitosan, collagen, gelatin, silk fibroin, keratin, elastin, hyaluronic acid, and resilin, are primarily extracted from biological byproducts such as crustacean shells, animal hides, feathers, and connective tissues. Their structural and functional properties make them appropriate for a wide range of applications in biomedicine, pharmaceuticals, environmental management, and packaging industries. This chapter explores the journey of these biopolymers, beginning with their chemical composition, physical and biological properties, raw material sources and extending to their development processes. Along with traditional methods of extraction and purification, ecofriendly and scalable methods such as enzymatic treatments, supercritical CO₂ extraction, ion exchange chromatography and membrane-based purification have been mentioned that enhance the purity and performance of the biopolymers while minimizing environmental impact. The multifunctionality of these materials is highlighted through their roles in tissue engineering, antimicrobial systems, drug delivery, and wound healing. Although these materials offer promising alternatives to synthetic polymers, challenges remain in terms of source variability, immunogenicity, and regulatory acceptance. Continued advancements in biotechnology, recombinant protein synthesis, and green chemistry are expected to expand their applicability and economic viability. Overall, animal-derived biopolymers represent a sustainable platform for next-generation material science and innovation, fostering a circular bioeconomy.

Keywords Animal-derived biopolymers • Biodegradability • Chitin-Collagen • Silk-keratin • Extraction techniques • Sustainable applications

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1 Introduction

Biopolymers are composed of repeating monomeric units joined together and generated by living organisms or derived from renewable biological sources [1]. These materials include various substances generated from plants, microbes, and animals, providing a versatile alternative to traditional fossil fuel-based polymers. Their biodegradability, renewability, and biocompatibility render them essential contenders in mitigating environmental issues and promoting a circular economy [2, 3].

Biopolymers have been used since ancient times when natural materials like rubber and starch were used for different applications [4]. For example, the Egyptians and Greeks frequently used collagen-rich animal tissues to heal wounds, a practice that gave way to modern biomedical applications of collagen and gelatin [5]. Silk fibroin has a long, illustrious history, especially in Asia. Silk manufacture in China originated around 5,000 years ago and remained a closely protected secret for generations. The biological application of silk as sutures and wound dressings dates back to ancient surgical procedures [6]. These biopolymers were substituted by chemically synthesized polymers owing to their enhanced cost-effectiveness, strength, and adaptability after the World War II and the advent of industrial revolution. Synthetic polymers are artificially produced via chemical synthesis using petroleum-derived monomers. Although they possess superior mechanical qualities and facilitate processing, they are predominantly non-biodegradable, hence not environmentally viable [7]. However, in recent decades, interest in the manufacture of biopolymers has increased significantly due to concerns regarding environmental sustainability [8, 9].

Polymers are broadly categorized into two main groups based on their origin and method of synthesis: biopolymers and synthetic polymers. Biopolymers are naturally occurring or biologically derived polymers that can be further divided into two subcategories: 1. Natural biopolymers, which are directly extracted from living organisms (such as plants, animals, or microbes) with minimal chemical modification; and 2. Synthetic biopolymers, which are artificially synthesized through biotechnological or chemical processes to mimic the structure or function of natural biopolymers [10]. These things are made in a lab, yet they are meant to look like or work with biological systems. Polylactic acid (PLA) and polycaprolactone (PCL) are two examples of biodegradable materials that come from renewable resources. Biomedical gadgets, packaging, and farming use these materials a lot [11]. In contrast, synthetic polymers like polyethylene, polypropylene, and polystyrene are entirely man-made, artificially produced via chemical synthesis using petroleum-derived monomers; and are often not biodegradable (Fig. 1).

Natural biopolymers can be further divided into three groups based on where they come from: animals, plants, or microbes. Natural polymers of animal and plant origin are again divided into proteins and polysaccharides, while lipid-based polymers form a smaller but functionally important category [12, 13]. Collagen, gelatin, keratin, silk fibroin, etc. are a few protein-based biopolymers that come from animals. These

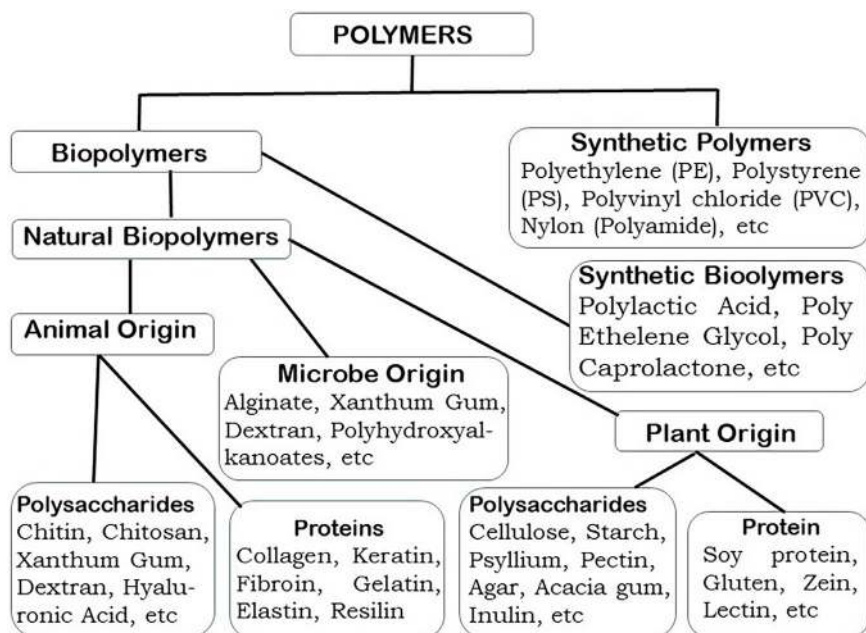


Fig. 1 Schematic representation of classification of polymers

materials have both structural and functional roles in their natural biological environments [14]. Today, they are frequently used in biomedical applications because they are biocompatible and biodegradable. Plant proteins like zein from corn and gluten from wheat have also gotten a lot of attention for use in food packaging and pharmaceutical industries [15].

Polysaccharides form another major class of natural polymers. From animals, chitin and its deacetylated derivative chitosan, commonly found in the exoskeletons of crustaceans, have gained attention for use in drug delivery, water treatment, and antimicrobial films [16]. Cellulose, starch, and pectin are all types of plant polysaccharides that are plentiful and may be utilized over and over again. They are used in textiles, food, and paper [16]. Microbial polysaccharides like dextran, xanthan gum, and alginate (some come from algae, but others are made by microbes) are very useful in food thickeners, wound dressings, and controlled release systems [17]. Lipid-based polymers are a smaller but nonetheless important type of natural polymers. They include cutin and suberin, which are present in plant cell walls, and waxes that animals like bees make. In nature, these polymers protect things, and scientists are looking at their ability to repel water and form barriers in biodegradable coatings and packaging materials [18].

Animal-derived biopolymers constitute a major class of natural polymers that have drawn renewed interest due to their unique properties including biodegradability, biocompatibility, and environmental sustainability. These renewable materials can easily be naturally broken down into harmless products such as biomass and water; and thus contribute less to greenhouse gas emissions compared to conventional polymers [19].

As sustainability has become increasingly important, researchers have made remarkable progress in developing new and better ways to extract and improve biopolymers, opening up exciting new uses for these materials. Many experts now see them as alternative replacements for traditional polymers, helping us build a greener tomorrow [20]. Current research indicates that while animal-derived biopolymers possess exceptional properties for applications in food packaging, biomedicine, and pharmaceuticals, they remain less explored than their plant-derived counterparts [19, 21]. This chapter takes a comprehensive look at animal-based biopolymers, categorizing them according to their chemical composition, physical and chemical behaviors, biological activity, and the various animal sources they come from, whether from ocean creatures, farm animals, or insects. The extraction of the animal-derived biopolymers, along with purifying processes has also been included.

1.1 Chitin

Chitin is a natural, sugar-based compound found in the exoskeletons of crustaceans, insects, and in the cell walls of fungi. As the second most common natural polymer after cellulose, it's vital in nature and offers a ton of potential for uses in medicine, farming, and environmental solutions. This response dives into what makes chitin special, exploring its physical and chemical traits, as well as its biological activity [22, 23].

1.1.1 Chemical Composition and Molecular Structure

Chitin is composed of repeating N-acetyl-D-glucosamine units, linked through β -(1 $\rightarrow$ 4) glycosidic bonds making up a linear polymer backbone. The general formula can be represented as $(C_8H_{13}O_5N)_n$, where “n” indicates the degree of polymerization [24] (Fig. 2).

Chitin is organized into highly crystalline microfibrils, which can exist in three polymorphic forms: (i) α -chitin: antiparallel chains, the most stable and common form found in crustaceans; (ii) β -chitin: parallel chains, found in squid pens; and (iii) γ -chitin: a mix of parallel and antiparallel chains, less common. The strong hydrogen bonding between chains in α -chitin contributes to its high tensile strength, insolubility and resistance to enzymatic degradation, characteristics that are essential for its biological functions [26, 27].

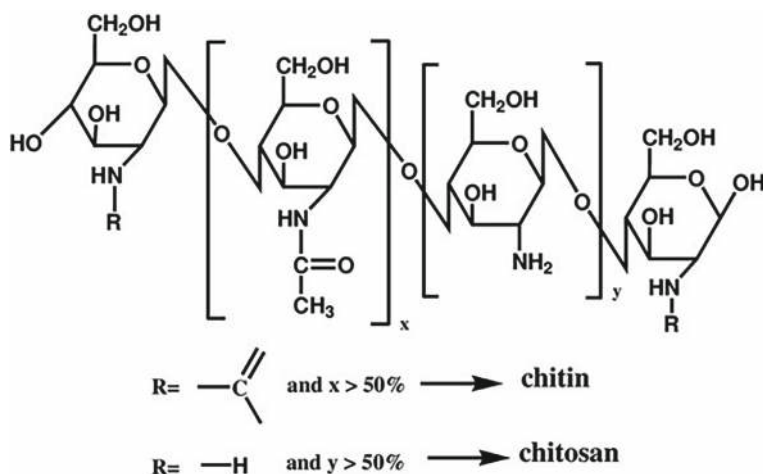


Fig. 2 A simplified, abstract diagram of chemical structure of chitin and chitosan [25]

1.1.2 Physicochemical Properties

Solubility

Chitin is less soluble in water that makes its difficult extract it for different uses. But, when deacetylated, it turns into chitosan which is soluble in acidic solutions due to the presence of protonated amino groups [26]. The crystalline structure of chitin is the main roadblock to its solubility; treating it with alkaline solutions or certain enzymes can make it more soluble [27].

Biodegradability

Chitin is ecofriendly and can be easily broken down naturally by enzymes called chitinases produced by various microbes. These enzymes break down chitin into non-toxic products like glucosamine, which boost helpful microbial activity in the environment [23]. The biodegradation of chitin depends on the degree of acetylation, influencing its persistence in the environment [26].

Mechanical Strength

Chitin exhibits great mechanical strength because of its fibrous, crystalline makeup. This property makes it a natural choice for structural roles in biological systems that require rigidity and protection [28]. Composites made from chitin combined with

other materials like cellulose or chitosan showed enhanced mechanical strength, making them perfect for use in various range of applications [29].

Thermal Properties

Chitin is robust to heat and withstand temperatures approximately up to 300 °C before it starts to break down. This thermal stability makes it a great candidate for processes that involve high temperatures, keeping it reliable where other materials might fail [30, 31].

1.1.3 Bioactivity

Biocompatibility

Chitin and its derivatives, particularly chitosan, are known for their biocompatibility, making them suitable for various biomedical applications, including wound dressings and tissue engineering scaffolds. They promote cell adhesion and tissue growth [28, 32]. Immune response studies suggest minimal inflammatory reactions associated with chitin-based materials, enhancing their applicability in medical settings [33].

Antimicrobial Properties

Chitin demonstrates antimicrobial properties, which can be enhanced in its deacetylated form, chitosan. The positive charge on chitosan allows for ionic interactions with negatively charged bacterial cell walls, exhibiting inhibitory effects against a range of pathogens [33, 34]. Studies have highlighted the potential of chitin and chitosan composites for deploying antimicrobial activity through the incorporation of nanoparticles or other bioactive agents [35].

1.1.4 Sources of Chitin

Chitin is the second most abundant biopolymer in nature, primarily sourced from [22, 36, 37].

- i) *Marine Crustaceans*: Such as shrimp, crab, and lobster shells; these are the most common commercial sources due to high chitin content and availability as seafood waste.
- ii) *Insects*: Present in the exoskeletons of various insects.
- iii) *Fungi*: Found in the cell walls of many fungal species, especially zygomycetes and ascomycetes.
- iv) *Mollusks*: Present in the radulae and structural parts of some mollusks.

These sources vary in chitin purity and structural form (e.g., α -chitin from crustaceans vs. β -chitin from squid).

1.1.5 Extraction Processes

The extraction of chitin primarily derived from crustacean shells consists of several critical processes, typically involving deproteinization, demineralization, and hydrolysis.

Deproteinization

This is a vital first step in isolating chitin from its source, as it removes proteins and other organic contaminants that may interfere with the purity of the chitin extracted. There are many different ways to achieve this including chemical treatments involving treatment with alkaline solutions like sodium hydroxide (NaOH). It has been also reported that acetic acid treatment at 7.5% yield chitin without risking severe depolymerization [38, 39]. To minimize the impact of hazardous chemicals, an environment friendly method involving use of some specific proteases is often used which selectively break down the proteins while preserving the integrity of the chitins [40].

Demineralization

This is the next step after deproteinization, which is done to remove the excess mineral content, mainly calcium carbonate (CaCO_3), which can affect the structural integrity of chitin. This is done by treating the material with dilute acids like hydrochloric acid (HCl) or citric acid. This step is done in a careful and controlled manner allowing the acids to react and dissolve the inorganic minerals, and avoid over hydroxylation of chitin [40, 41].

1.1.6 Purification Techniques

The purification of chitin involves multiple techniques done to remove the residual proteins, minerals, and pigments. The extracted chitin typically undergoes bleaching processes to achieve necessary purity levels, that makes it more useful for use in various applications, including pharmaceuticals and biomaterials [41]. New methods like use of non-toxic natural deep eutectic solvents have proved to gently extract and purify chitin without significant chemical degradation, making it more biocompatible and functional [42].

The source of the chitin like crab shells or fungal cell walls along with the selected methods regulate the extraction and purification process of chitin [28, 32]. Traditional

methods, while effective, are often criticized for their environmental impact due to harsh chemicals and conditions that can harm polymer integrity [43]. Therefore, few new ecofriendly methods like use of supercritical CO₂ and microbial fermentation have come up but require optimization for improved yield and efficiency [44].

1.2 Chitosan

Chitosan represents a deacetylated derivative of chitin, produced through alkaline deacetylation processes that remove acetyl groups from the N-acetyl-D-glucosamine units, introducing free amino groups (–NH₂) in the structure that significantly alters its chemical structure and properties. This change increases its solubility in acidic solutions and also increases the biocompatibility and potential applications in various fields [45, 46].

1.2.1 Chemical Composition and Molecular Structure

The primary characteristic of chitosan is its amino polysaccharide structure, which can be described using its molecular formula, typically approximated as (C₆H₁₁O₄N)_n, where “n” indicates the degree of polymerization. A simplified, abstract diagram of chemical structure of chitosan is provided in Fig. 1. The presence of amino groups contributes to chitosan’s ability to form hydrogen bonds and facilitate interactions with various biological systems [46]. Furthermore, chitosan’s molecular weight varies according to the source and extraction process, influencing its physicochemical properties and functionality [47].

1.2.2 Physicochemical Properties

Solubility

The protonation of the amino groups present in Chitosan in acidic conditions (pH < 6) makes it highly soluble. This enhanced solubility of chitosan is utilized in various applications, including drug delivery and food preservation [48].

Biodegradability

Chitosan, as its cousin chitin, demonstrates exceptional biodegradability, primarily due to its susceptibility to microbial degradation and enzymatic hydrolysis. This makes chitosan an ideal candidate for environmentally friendly applications such as food packaging, medical applications, etc. [49].

Mechanical Strength

The mechanical strength of chitosan depends on its molecular weight, degree of acetylation, and processing conditions [50, 51]. Composite materials like those combined with lignin or graphene, have shown superior mechanical properties due to stronger interactions among their components. Still, chitosan is used in manufacture of different films and fibers with high tensile strength, which are used for various biomedical applications such as sutures, scaffolds, and drug delivery systems [52, 53].

Thermal Properties

Chitosan is lesser stable to heat compared to chitin and it starts breaking down at temperatures between 200 °C and 300 °C. Modifications through cross-linking or blending can improve its thermal stability, making it suitable for various high-temperature applications [54, 55].

1.2.3 Bioactivity and Functional Attributes

Biocompatibility

Chitosan is recognized for its biocompatibility, which facilitates cell adhesion, proliferation, and differentiation. This characteristic is especially crucial in tissue engineering, where chitosan scaffolds encourage tissue regeneration and repair [56].

Antimicrobial Properties

Chitosan exhibits significant antimicrobial activity against a range of pathogens, including bacteria and fungi. Its mechanism involves electrostatic interactions between the positively charged chitosan and the negatively charged bacterial cell membranes, disrupting their integrity and leading to cell death [48, 57]. Incorporating chitosan into films or coatings has been shown to enhance the antimicrobial properties of packaging materials, thereby extending the shelf life of food products [58].

1.2.4 Sources of Chitosan

Chitosan is obtained primarily from the following sources.

Crustacean Shells

The most common source of chitosan is the shells of crustaceans such as shrimp and crabs. The abundant waste generated from seafood processing provides a sustainable raw material [46, 59].

Fungal Sources

Recent studies have indicated that fungi, such as *Aspergillus niger*, can also be a valuable source of chitosan. The advantages of fungal chitosan include a lower risk of allergens and a more sustainable and year-round production capability as it is not dependent on seasonal harvesting [59, 60].

Insect Exoskeletons

Chitosan can also be extracted from insects, such as mealworms (*Tenebrio molitor*) and houseflies (*Musca domestica*), offering an alternative source that aligns with the growing interest in insect proteins and waste management [41, 56].

1.2.5 Processes of Extraction

The extraction of chitosan generally involves a few key steps aimed at converting chitin into chitosan.

Deproteinization

Initially, the source material undergoes deproteinization, often using alkaline solutions (e.g., sodium hydroxide) at elevated temperatures to remove proteins associated with chitin. This step is critical in ensuring the purity and quality of the chitosan [60, 61].

Demineralization

Following deproteinization, acids (commonly hydrochloric acid) are used to remove minerals and other unwanted substances from the chitin, resulting in a more pure form called chitosan [60, 62].

Deacetylation

The crucial step in transforming chitin into chitosan is deacetylation, wherein chitin is treated with a concentrated alkaline solution (such as 50% NaOH) under heat. This reaction removes acetyl groups, resulting in the formation of chitosan with amino groups that enhance its solubility in acidic conditions [41, 63].

Filtration and Concentration

After extraction, the mixture is often filtered to separate chitosan from other impurities. The resulting chitosan solution can be concentrated as needed [59, 64].

1.2.6 Purification Techniques

Purification is essential to remove residual proteins, pigments, and other contaminants. Several methods are typically employed.

Dialysis

This procedure involves placing the chitosan solution in dialysis tubing to remove low-molecular-weight impurities and residual acids from bigger chitosan molecules, increasing purity of chitosan without altering its molecular structure [65].

Precipitation

Chitosan is isolated in a more pure and concentrated manner by adding alcohol or other solvents, which separate it from low-molecular-weight contaminants [63, 66].

Ultrafiltration

This another method used in purification of chitosan using a semi-permeable membrane that retains high-molecular-weight chitosan while allowing smaller impurities and solvents to pass through making it purer and more concentrated [59, 67].

Membrane Filtration Techniques

Some studies have explored the use of chitosan membranes in filtering and purifying solutions containing chitosan, achieving high purification coefficients [66].

Chemical Modifications

After purification, chitosan may be chemically modified by adding some functional groups to improve its properties like solubility, reactivity, etc. for specific applications, such as drug delivery, water treatment, or biomedical devices [68, 69].

1.3 Collagen

Collagen is an essential structural protein found in various animal tissues, including skin, tendons, ligaments, bones, and cartilage. It constitutes about 25%-30% of the total protein content in the human body, playing critical roles in cell adhesion, tissue integrity, and mechanical stability. This response details the chemical composition and molecular structure, physicochemical properties, and bioactive attributes of collagen.

1.3.1 Chemical Composition and Molecular Structure

Collagen is primarily composed of amino acid chains, with a prominent repeating sequence of glycine-proline-X or glycine-X-Y, where X and Y can be any amino acid but often include proline and hydroxyproline [70, 71]. The primary structure dictates the protein's secondary structures, where collagen typically forms a triple-helix structure consisting of three polypeptide chains winding around each other. Collagen type I, the most abundant form, features this triple helix as a key structural feature, providing strength and elasticity [72, 73].

In terms of broader molecular weights, collagen can be extracted in various forms (e.g., native, denatured), influencing its biocompatibility and mechanical properties. For example, native collagen maintains a higher molecular weight, contributing to its unique characteristics, while denatured collagen is often used in injections and surgical procedures, providing flexibility and adjustability [74] (Fig. 3).

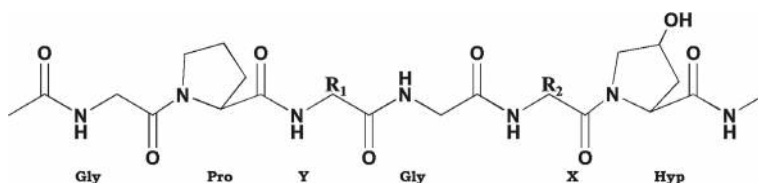


Fig. 3 A simplified, abstract diagram of collagen type-I

1.3.2 Physicochemical Properties

Solubility

The solubility of collagen varies depending on its type and form. Native collagen is generally insoluble in water but can be solubilized in acidic or enzymatic solutions (e.g., pepsin treatment). The resulting gelatin form of collagen is soluble and often used in various food and pharmaceutical products [75].

Biodegradability

Collagen is biodegradable and it naturally breaks down with the action of enzymes like collagenases. This property is essential for its applications in tissue engineering, where it provides a temporary scaffold that is gradually replaced by native tissue. The rate of degradation varies based on cross-linking methods and environmental conditions [76].

Mechanical Strength

Collagen is highly tensile, making it perfect for a structural role in tissues that need to hold up under pressure, like tendons and ligaments. The mechanical strength of it comes from the triple-helix structure of the collagen which resist stretching and impact [77]. However, the mechanical strength of collagen material vary based on the collagen type (e.g., type I, II, or III) and specific processing methods (e.g., cross-linking) employed [76].

Thermal Properties

Collagen can handle heat pretty well showing moderate thermal stability, with denaturation occurring around 37 to 60 °C, depending on its form and environmental conditions (pH, ionic strength). Denatured collagen forms gelatin upon heating, which can further be tailored for various applications [72].

1.3.3 Bioactivity and Functional Attributes

Biocompatibility

Collagen is renowned for its high biocompatibility, leading to minimal immune response upon implantation. It promotes cell adhesion, proliferation, and differentiation, making it ideal for various biomedical applications involving tissue scaffolds and wound healing [78, 79].

Antimicrobial Properties

While not primarily known for antimicrobial characteristics, collagen can be enhanced with antimicrobial agents or incorporated into composites to confer these properties. Such modifications can be significant in wound dressings and surgical meshes to reduce infection rates [80].

1.3.4 Sources of Collagen

Collagen is primarily derived from animal tissues, notably skin, bones, and connective tissues from various species. The most commonly utilized sources include bovine (cow), porcine (pig), and marine organisms, particularly fish such as cod and other marine species [81]. Marine sources have gained preference due to their reduced risk of disease transmission and lower immunogenicity compared to terrestrial sources [82]. The availability of collagen from jellyfish and sea cucumbers is also being explored, particularly for their unique properties and ease of extraction [83, 84].

1.3.5 Extraction Processes

The extraction of collagen typically involves several defined steps.

Pretreatment

Since collagen is extracted from animal bodies, this step is carried out that involves enzymatic, acid, or alkaline treatments of the source material to remove non-collagenous proteins, fats, and minerals. Enzymatic pretreatment is done using proteolytic enzymes that removes unwanted proteins without damaging the collagen itself [85]. Similarly acid-soluble forms of collagen are commonly obtained from the skin through acid treatment [86].

Solubilization

After pretreatment, collagen is solubilized into a solution, commonly using acidic solutions (like acetic acid) or neutral pH buffers, allowing for the release of collagen while maintaining its triple-helix structure [81, 87].

Filtration and Centrifugation

This step is crucial for ensuring the purity of extracted collagen. After solubilization, the collagens are subjected to filtration and centrifugation to separate the collagen solution from undissolved impurities and residual cellular components [88].

1.3.6 Purification Techniques

Following extraction, several purification processes can be employed to achieve high-purity collagen.

Ultrafiltration

Ultrafiltration membranes separate molecules based on size and increase the concentration of collagen by retaining high-molecular-weight proteins while allowing smaller impurities to pass through [84].

Dialysis

This purification method involves the use of a semi-permeable membrane to remove low-molecular-weight contaminants and retain collagen within a specific molecular weight range [89]. This method aids in the removal of excess salts and small peptides, enhancing collagen purity [90].

Chromatographic Methods

This involves the use of ion-exchange chromatography for separating different collagen types based on charge differences that can refine the collagen and concentrate it [85].

Lyophilization

After purification, collagen solutions can be freeze-dried (lyophilized) to produce stable powders that are easy to store and transport. Lyophilization also facilitates the conversion of collagen into scaffold forms suitable for tissue engineering applications [5, 87].

Cross-Linking and Modification

To improve the collagen's strength and compatibility with the body, cross-linking with other biomaterials and other chemical modifications are often done to make it more suitable for uses like hydrogels in drug delivery or wound healing treatments [91].

1.4 Gelatin

As chitosan is derived from chitin, similarly gelatin is derived from hydrolysis of collagen, primarily sourced from animal connective tissues, skin, and bones. It is widely utilized in food, pharmaceutical, and biomedical applications due to its unique physicochemical properties and biocompatibility [50].

1.4.1 Chemical Composition and Molecular Structure

Gelatin is mostly made up of amino acids like glycine, proline, and hydroxyproline, which contribute to presence of high proportion of hydrophilic regions. This makes it highly soluble; essentially, it's the soluble version of collagen, made up of long polypeptide chains that form when collagen gets denatured, or broken down, through heating [92, 93].

Molecular Formula: Gelatin does not have a specific formula of itself due to its variable molecular weight. But to describe technically, it has a repeating units of amino acids with a general composition of $C_6H_{11}O_4N$ structure as shown in Fig. 4 [92].

Structure: Gelatin has a flexible structure and it can shift between a loose, random coil and a tight triple-helix shape, depending on things like temperature or concentration. Upon cooling, gelatin can form a gel, a state that is exploited in many applications, particularly in food products and tissue engineering scaffolds. The molecular

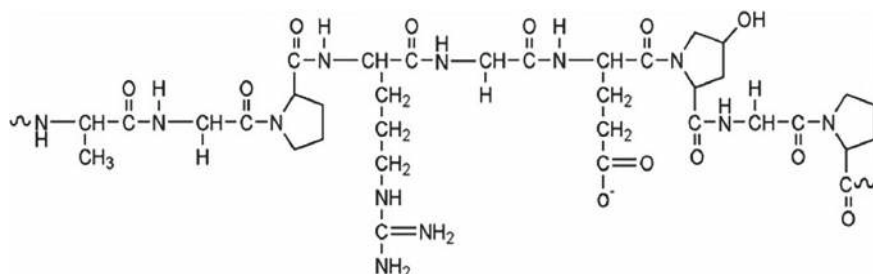


Fig. 4 A simplified, abstract diagram of gelatin polymer [94, 95]

structure of gelatin therefore allows for significant elasticity and resilience in gels formed from it [92, 94].

1.4.2 Physicochemical Properties

Solubility

Gelatin dissolves in various aqueous solutions of acids, making it versatile to be used in different applications. It is soluble in water at warmer temperatures (typically above 40 °C) and forms a gel upon cooling. This temperature-dependent solubility is a critical feature for various culinary and pharmaceutical applications [94, 96].

Biodegradability

Gelatin is biodegradable and can be hydrolyzed by peptidases and collagenases, resulting in non-toxic products like amino acids and peptide fragments that can be utilized by cells. This property allows it to be used in temporary scaffolds for tissue engineering and regenerative medicine [94].

Mechanical Strength

While its precursor- Collagen is highly tensile, gelatin has low mechanical strength compared to all other biopolymers. But is adequate for various applications when properly formulated. Its tensile strength and viscoelastic properties can be increased by cross-linking with other materials or by incorporating bioactive compounds [92, 96].

Thermal Properties

Gelatin is more thermally stable than collagen, with denaturation occurring above 100 °C temperature, where it transitions from a gel state. The thermal behavior varies based on gel-forming conditions and the molecular weight of the gelatin used [94, 96].

1.4.3 Bioactivity and Functional Attributes

Biocompatibility

Gelatin is well-known for its biocompatibility, making it suitable for medical applications. In studies, gelatin supports cell adhesion, proliferation, and differentiation, thus

serving as an effective scaffold in tissue engineering [92]. Its low immunogenicity and antigenicity contribute to its favorable acceptance in biological environments [93].

Antimicrobial Properties

Gelatin itself exhibits limited antimicrobial properties; however, it can be combined with various antimicrobial agents to enhance its efficacy. For instance, hybrid scaffolds containing gelatin and bioactive agents like silver nanoparticles or essential oils have demonstrated enhanced antimicrobial activity [97].

1.4.4 Sources of Gelatin

Gelatin is predominantly derived from the hydrolysis of collagen, which is found in the connective tissues, skins, and bones of animals. Common sources include.

Porcine and Bovine Tissues

These are traditional sources of gelatin, particularly from skin, bones, and tendons, making up a significant portion of the market [98, 99].

Fish Skins and Bones

Due to lower religious and ethical concerns, gelatin from fish is increasingly utilized, particularly in regions where porcine or bovine sources are restricted [100]. Fish gelatin often exhibits different gelling properties compared to mammalian gelatin, which can be beneficial for specific applications [98].

Chicken Byproducts

Research has indicated that gelatin can also be extracted from chicken byproducts, which are often abundant from poultry processing industry waste [101].

1.4.5 Processes of Extraction

The extraction of gelatin is a multistep process involving the transformation of collagen into gelatin.

Preparation of Raw Materials

This involves the cleaning and removal of non-collagenous materials from the raw source (e.g., skins or bones). The preparation largely dictates the yield and quality of gelatin [100].

Acid or Alkaline Treatment

The raw material is usually treated with an acid (e.g., acetic acid) or an alkaline solution to effectuate the swelling of collagen and facilitate its hydrolysis into gelatin. The treatment conditions (pH and temperature) significantly influence the gelatin yield and properties [99, 101].

Heating

After the initial treatment, the collagen is subjected to heating, typically between 60 °C to 100 °C, to solubilize collagen into gelatin. Heating methods can vary (e.g., steaming, boiling), impacting the extraction efficiency and the characteristics of the final product [102].

Filtration

Following solubilization, the mixture is filtered to remove insoluble impurities, including residual fat, pigments, and non-collagen proteins. This filtration step is crucial for obtaining a clear gelatin solution [103].

1.4.6 Purification of Gelatin

Purification processes help in refining the extracted gelatin to enhance its suitability for various applications. This is done by various processes as mentioned earlier sections of purification of chitin or gelatin using dialysis [103], precipitation [103], ultrafiltration [104], and freeze-drying [99].

1.5 Silk Fibroin

Silk fibroin is a natural protein derived from the cocoons of silkworms, primarily *Bombyx mori*, and is recognized for its exceptional mechanical properties and biocompatibility, making it a versatile material for various biomedical applications. This response provides a detailed overview of silk fibroin's chemical composition

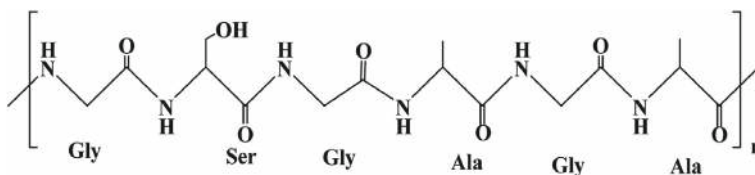


Fig. 5 A simplified, abstract diagram of silk

and molecular structure, physicochemical properties, as well as its bioactivity and functional attributes.

1.5.1 Chemical Composition and Molecular Structure

Silk fibroin primarily comprises two proteins: fibroin (the structural component) and sericin (the protective gum). The main structural unit of silk fibroin is a long-chain polymer composed of repeating amino acid sequences, rich in glycine, alanine, and serine. Approximately two-thirds of the amino acids in silk fibroin are glycine (Gly), contributing to its unique flexibility [105]. The molecular structure of silk fibroin is characterized by a highly organized secondary structure, predominantly consisting of β -sheet crystals, which provides strength and stability [106, 107].

The molecular weight of silk fibroin can range from approximately 200 kDa to several million Daltons, depending on the source and extraction methodology employed. Processing conditions can affect the structural configuration, where silk's conformation can switch from random coil to ordered β -sheet structures, markedly enhancing its mechanical properties [108] (Fig. 5).

1.5.2 Physicochemical Properties

Solubility

Silk fibroin is generally water insoluble but can be dissolved in solutions containing lithium bromide or formic acid, which allow molding it into various formats such as films, gels, and scaffolds. The solubility can be regulated based on application requirements [109].

Biodegradability

Silk fibroin is biodegradable, and its degradation can be modulated via enzymatic action or hydrolysis. The degradation rate varies based on molecular weight and the degree of crystallinity in the fibroin; higher crystallinity generally leads to slower

degradation [110]. This property is particularly advantageous for scaffolds used in tissue engineering.

Mechanical Strength and Thermal Properties

Silk fibroin exhibits remarkable mechanical strength, akin to that of some synthetic polymers. Its tensile strength can be attributed to its crystalline β -sheet structure, which endows the protein with both elasticity and toughness [111]. In terms of thermal properties, silk fibroin remains thermally stable up to about 200 °C, where it retains its properties without significant degradation [107].

1.5.3 Bioactivity

Biocompatibility

Silk fibroin is well-regarded for its outstanding biocompatibility, making it suitable for a range of medical applications, including wound healing and tissue engineering. It promotes cell adhesion, proliferation, and differentiation, which are crucial for successful integration into biological systems [112].

Antimicrobial Properties

Research indicates that silk fibroin exhibits mild antimicrobial properties. This characteristic can be enhanced through functionalization with antimicrobial agents or incorporation with other materials to combat microbial infection in areas such as wound healing [109, 113].

1.5.4 Sources of Silk Fibroin

Silkworm Cocoons

The primary source of silk fibroin is the cocoons produced by the domesticated silkworm *Bombyx mori*. These are cultivated at large scales in sericulture industries, making them the most common and commercially viable source [114].

Other Insect Sources

While *Bombyx mori* is the most widely studied, silk fibroin can also be extracted from other insect species, such as *Antheraea mylitta* (Tasaar silk) and *Philosamia ricini*

(Eri silk). These non-mulberry silks exhibit different properties and compositions that may be advantageous for certain applications [115].

Spider Silk

Spider silk fibroin is another potential source due to its superior tensile strength; however, its extraction poses challenges as spiders do not produce silk in quantities comparable to silkworms [116].

1.5.5 Processes of Extraction

The extraction of silk fibroin from cocoons involves several key steps.

Degumming

The first step in the extraction process is degumming, which involves removing sericin, a glue-like protein that coats the silk fibers. That is done by boiling the silk in an alkaline solution (e.g., sodium carbonate) or by using proteolytic enzymes [117].

Solubilization

After degumming, the silk fibers are dissolved in a concentrated lithium bromide (LiBr) solution, and left at around 60 °C for several hours. This step helps to solubilize the fibroin while leaving behind any remaining sericin. The use of LiBr is crucial because it effectively breaks down the silk fibroin's tertiary structure without denaturing the protein [118].

Filtration and Centrifugation

Following solubilization, the solution is filtered to remove undissolved particles and impurities. Subsequently, centrifugation may be employed to enhance the separation of soluble silk fibroin from any residual debris [119].

1.5.6 Purification Techniques

The purification of silk fibroin is essential for achieving high-quality biopolymers suitable for biomedical applications.

Dialysis

After solubilization, the silk fibroin solution is dialyzed against deionized water to remove lithium bromide and other small molecular impurities. This step enhances the purity of the silk fibroin, making it appropriate for various applications [118].

Desalting

This process involves the removal of excess salts. Various methods are available for desalting the silk fibroin solution, including the use of ultrafiltration or isopropanol extraction, and are done in a controlled manner to prevent any damage to the silk. Recent advancements in using ternary systems (e.g., CaCl_2 -ethanol-water) for accelerated desalting have shown promise in simplifying the purification procedure without denaturing fibroin [120].

Lyophilization

Once purified, silk fibroin can be freeze-dried (lyophilized) to obtain a stable powdered form. This method preserves the protein's molecular structure and makes it easier to store and handle for later use [115].

Characterization Techniques

Characterization of the purified silk fibroin involves using spectroscopic methods, such as Fourier transform infrared (FTIR) spectroscopy, to confirm the presence and structural integrity of the protein. These assays ensure that the silk fibroin has retained its β -sheet conformation, which is crucial for its mechanical strength and biological activity [121].

1.6 Keratin

Keratin represents a structural protein with fibrous characteristics found throughout different animal tissues, such as hair, nails, feathers, and skin's outer layers. This protein offers mechanical strength and protective functions, making it valuable for biomedical uses like wound treatment, tissue development, and pharmaceutical delivery methods.

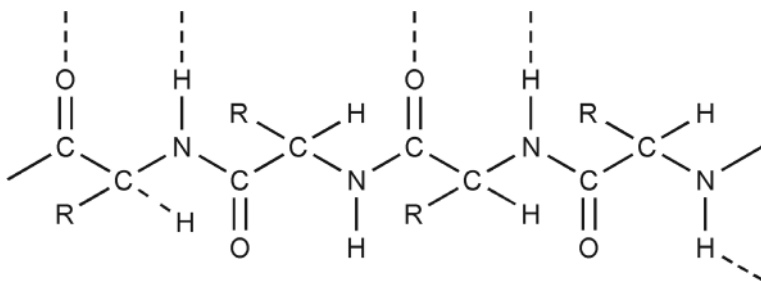


Fig. 6 A simplified, abstract diagram of keratin polymer

1.6.1 Chemical Composition and Molecular Structure

Keratin is a tough, fibrous proteinaceous biopolymer made up of long polypeptide chains which are rich in cysteine amino acid that form strong disulfide bonds which are crucial for keratin's structural integrity and durability. It can be classified into two types: α -keratin and β -keratin; where α -keratins are predominantly found in hair and skins of mammals and are composed of coiled-coil structures. Whereas β -keratins are found in feathers and nails of birds and reptiles and consist of tightly packed β -sheets, resulting in greater rigidity [122, 123].

The molecular structure of keratin involves polypeptide chains weaving together a strong, web-like intermediate filament networks that give tissues like hair and nails their toughness. These filaments can vary in size and organization and are responsible for the tensile strength and durability of keratinous tissues [124]. The structural properties of keratin can be influenced by post-translational modifications, including phosphorylation and glycosylation, which affect solubility and filament dynamics [125] (Fig. 6).

1.6.2 Physicochemical Properties

Solubility

Keratin is generally insoluble in water and most organic solvents due to its highly cross-linked structure containing substantial disulfide bonds. However, keratin can be made soluble through various treatments, including chemical hydrolysis, reduction of disulfide bonds, and enzymatic processing. Soluble keratin extracts, such as those derived from feathers, exhibit high hydrophilicity, which is advantageous for biomedical applications [122, 126].

Biodegradability

Keratin is considered biodegradable under microbial action, particularly by keratinase-producing fungi and bacteria. This property reinforces its suitability for environmental applications, such as biodegradable films and scaffolds [126, 127].

Mechanical Strength and Thermal Properties

Keratin exhibits significant mechanical strength, attributable to its fibrous structure and intermolecular interactions. However, the mechanical properties can vary based on the source and method of extraction. Soluble keratin typically shows reduced mechanical strength compared to its insoluble counterparts, which retain higher structural integrity due to disulfide cross-linking. Thermally, keratin can undergo denaturation at elevated temperatures, typically above 200 °C [128, 129].

1.6.3 Bioactivity

Biocompatibility

Keratin is inherently biocompatible, making it suitable for tissue engineering and regenerative medicine. Studies have shown that keratin-based materials support cell adhesion and proliferation, facilitating the regeneration of various tissues [129, 130].

Antimicrobial Properties

Keratin has demonstrated antimicrobial efficacy, particularly when incorporated into composite materials. Studies have shown that keratin films can provide a suitable environment for antimicrobial agents, enhancing their effectiveness against bacterial infections [131].

1.6.4 Sources of Keratin

Animal Hair and Feathers

The most common sources of keratin are hair and feathers. Chicken feathers, for example, are abundantly available as byproducts of the poultry industry. Human hair is another source frequently used due to its availability and specific keratin properties [132, 133].

Wool

Another significant source of keratin is sheep wool, which contains high concentrations of keratin proteins. Wool keratin can be extracted for various applications in biomedicine and materials science [123, 130].

Horns and Claws

Keratin is also found in harder tissues like horns and claws of animals, providing a robust source for extraction. However, these sources are less commonly exploited than hair and feathers [130].

Recombinant Keratin

Advances in biotechnology have led to the development of recombinant keratin, where specific keratin proteins can be produced in microbial systems. This process offers a sustainable alternative to conventional source of keratin production [122].

1.6.5 Processes of Extraction

Mechanical Pretreatment

The source of keratin being animal feathers, nails and hairs, hence the first step of keratin extraction involve mechanical pretreatment that includes grinding, milling, or other physical disruption to increase surface area and facilitate chemical digestion that follows next [134].

Chemical Extraction

Chemical treatments are the most common method done for cleaning and removing non-keratinous material such as fats and debris for extracting keratin. Common approaches include.

2A. *Reduction*

Chemicals such as sodium sulfide or dithiothreitol are used to break disulfide bonds in keratin, facilitating solubilization [135].

2B. Oxidation

Oxidizing agents can also be employed to alter the keratin structure and enhance solubility [136].

2C. Hydrolysis

Alkaline (NaOH) or acidic hydrolysis (HCl) are frequently used to denature keratin, resulting in soluble keratin hydrolysates. Alkaline hydrolysis, particularly, has been utilized effectively in this regard [137, 138].

2D. Enzymatic Degradation

Proteolytic enzymes (like keratinase) are used to selectively break peptide bonds without harsh chemicals [123].

Microwave and Ultrasound-Assisted Extraction

Recently new and advanced technologies like microwave and ultrasound are used for extraction of keratin which has significantly reduced the extraction time along with increasing the yield. These methods utilize physical and thermal energy to disrupt keratin structures, promoting a higher solubilization rate [132, 138].

1.6.6 Purification Techniques

The keratin extracted from the above processes needs purification and increasing the concentration. Hence, the various techniques as mentioned in purification section of other biopolymers mentioned above namely chitin and gelatin are used, namely (a) filtration [135], (b) dialysis [123], (c) precipitation [138], (d) chromatographic techniques- that involves both ion exchange chromatography (mentioned in silk purification) and size exclusion size exclusion chromatography [134], (e) lyophilization and freeze-drying [139].

1.7 Hyaluronic Acid (ha)

Hyaluronic acid, or HA (sometimes called hyaluronan), belongs to the glycosaminoglycan family without sulfate groups and serves as a crucial element within connective tissue's extracellular matrix (ECM). Due to its exceptional characteristics and biocompatibility, HA has gained considerable attention in biomedical and pharmaceutical applications [140].

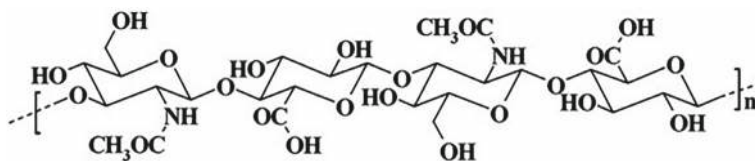


Fig. 7 A simplified, abstract diagram of Hyaluronic Acid (HA)

1.7.1 Chemical Composition and Molecular Structure

Hyaluronic acid is a linear polymer composed of repeating disaccharide units of β -(1,4)-D-glucuronic acid and β -(1,3)-N-acetyl-D-glucosamine. Each repeating unit contains one glucuronic acid and one N-acetylglucosamine, giving rise to its unique structure [141, 142]. The molecular weight of hyaluronic acid can vary widely, ranging from 5,000 to over 8,000,000 Da, which affects its viscosity and biological functions [143]. The high-molecular-weight forms are primarily found in connective tissues, providing mechanical support and hydration, while lower molecular weights are often used in drug delivery applications due to their improved tissue permeability [144, 145] (Fig. 7).

1.7.2 Physicochemical Properties

Solubility

HA is highly soluble in water and forms viscous solutions, attributed to its hydrophilic nature and ability to form hydrogen bonds with water molecules [141]. The solubility of HA remains relatively stable across different pH levels and ionic strengths, making it suitable for various formulations [145].

Biodegradability

Hyaluronic acid is biodegradable, primarily through the action of hyaluronidases, which can break down the polymer into smaller oligosaccharides. This property is particularly advantageous in medical applications, as it minimizes long-term foreign body reactions and supports tissue regeneration [142, 146].

Mechanical Strength and Thermal Properties

HA exhibits viscoelastic properties, enabling it to resist deformation and maintain structural integrity under load [143]. Cross-linked hyaluronic acid hydrogels can significantly enhance mechanical strength, making them useful as scaffolds in tissue

engineering [141, 146]. The thermal stability of HA is moderate, with degradation typically occurring at temperatures above 200 °C [147].

1.7.3 Bioactivity and Functional Attributes

Biocompatibility

HA is known for its excellent biocompatibility, making it suitable for a wide range of biomedical applications, including drug delivery systems, dermal fillers, and tissue engineering scaffolds. HA's inherent properties ensure it does not elicit significant immune responses [140, 144].

Antimicrobial Properties

Emerging studies have suggested that HA can enhance antimicrobial activity when used in conjunction with other agents, such as silver nanoparticles or antibiotics, effectively improving the overall efficacy of biomaterials designed for wound healing [148].

1.7.4 Sources of Hyaluronic Acid

Hyaluronic acid can be extracted from several biological sources.

Animal Tissues

Historically, HA has been extracted primarily from animal tissues such as rooster combs and the vitreous humor of bovine eyes. Rooster combs are particularly rich in HA and serve as a significant source for its extraction [149]. Bovine vitreous humor extraction has been utilized as well, although it presents challenges like contamination and lower yields [150].

Marine Organisms

Recently HA is extracted from marine sources, such as jellyfish, including species like *Acromitus octodentatus*. Marine extraction could potentially provide a more sustainable and ethical alternative to traditional animal-source methods [151].

Fermentation Processes

With the advancement in biotechnology bacterial fermentation using microorganisms such as *Streptococcus zooepidemicus* and *Xanthomonas campestris* are used for the production of HA. This method offers advantages in terms of scalability, ethical considerations, and reduced risk of contamination [152].

Plant Sources

Research on utilizing plant-based materials for HA production is ongoing, but there is less established evidence compared to other sources [153].

1.7.5 Processes of Extraction

The extraction of hyaluronic acid typically includes several key steps.

Preparation

For animal sources, the initial step usually involves cleaning and using enzymes such as papain or trypsin to break down proteins surrounding HA molecules, thus liberating HA from the tissue matrix [149].

Aqueous Extraction

The actual extraction involves treating the prepared material with a solvent, often water or a buffered solution, at elevated temperatures. This process allows for the solubilization of HA while leaving behind non-soluble contaminants [153].

Filtration

After aqueous extraction, the solution is filtered to remove solid residues, which may contain fats, proteins, and other impurities. This can be achieved through centrifugation or microfiltration techniques [153].

Precipitation

To concentrate and purify HA, alcohol (usually ethanol or isopropanol) is added to the filtered solution, resulting in the precipitation of HA. This method exploits HA's solubility characteristics to yield a more concentrated product [153].

1.7.6 Purification Techniques

After extraction of hyaluronic acid, purification is carried out to enhance the quality and usability of hyaluronic acid. The various techniques as mentioned in purification section of other biopolymers mentioned above namely chitin and gelatin are used, namely (a) filtration [149, 153], (b) dialysis [153], (c) precipitation [153], (d) chromatographic techniques- that involves both ion exchange chromatography (mentioned in silk purification) and size exclusion size exclusion chromatography [154], and (e) lyophilization and freeze-drying [153].

1.8 Elastin

Elastin is a biopolymer made up of structural proteins that is mostly present in the extracellular matrix of vertebrate connective tissues. It makes tissues like skin, lungs, arteries, and ligaments more flexible and strong, so they can stretch and shrink over and over again without changing shape permanently [155].

1.8.1 Chemical Composition and Molecular Structure

Elastin is primarily composed of polypeptide chains rich in glycine, proline, and valine, which facilitate its elastic properties. The protein's structure consists of cross-linked tropoelastin molecules, forming a resilient network that enables tissues to return to their original shape after stretching [156, 157]. The cross-linking primarily involves desmosine and isodesmosine, unique amino acids formed through the interaction of lysine side chains, which contribute to elastin's mechanical properties [157] (Fig. 8).

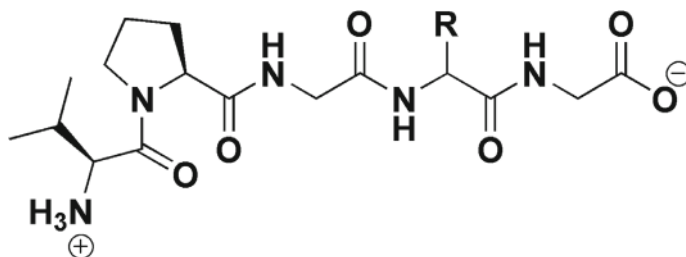


Fig. 8 A simplified, abstract diagram of elastin polymer

1.8.2 Physicochemical Properties

Solubility

Elastin is generally insoluble in water, primarily due to its fibrous structure and extensive cross-linking. It can be partially solubilized through enzymatic or alkaline treatments, which can break down the elastin structure, facilitating its use in various formulations [158, 159].

Biodegradability

A noteworthy characteristic of elastin, both in its native state and as elastin-like polypeptides (ELPs), is its biodegradability. Elastin degrades through enzymatic pathways involving proteolytic enzymes elastases, which play a significant role in maintaining tissue homeostasis and facilitating remodeling during physiological and pathological processes [159].

Mechanical Strength

Elastin possesses considerable tensile strength and elastic properties, allowing it to withstand significant mechanical forces while maintaining its integrity [156].

Thermal Properties

Elastin shows moderate thermal stability, retaining structural integrity at physiological temperatures but subject to denaturation above 100 °C [160].

1.8.3 Bioactivity

Biocompatibility

Elastin, as a biopolymer, exhibits remarkable biocompatibility, rendering it a significant element in numerous biomedical applications, especially in tissue engineering. The inherent presence of elastin in the extracellular matrix (ECM) facilitates the smooth integration of elastin-based materials with biological tissues, enhancing cell adhesion and proliferation while minimizing inflammatory responses. The biocompatibility of elastin is augmented by its minimal cytotoxicity and capacity to promote cellular processes, therefore aiding in tissue regeneration and repair [161].

Antimicrobial Properties

Recent studies have highlighted the potential of combining elastin with antimicrobial peptides (AMPs) to create functional biomaterials capable of combating microbial infections. For instance, elastin-like recombinant proteins can be engineered to include AMPs, which not only enhance antimicrobial activity but also retain the elasticity and resilience typical of elastin [160].

1.8.4 Sources of Elastin

Animal Tissues

The primary source of elastin is animal connective tissues, particularly in large quantities from the aorta, skin, lungs, and other elastic tissues. Common animal sources include bovine and porcine tissues [159, 162].

Broiler Skin

Research has explored elastin extraction from poultry skin, which is often discarded as waste. This method not only utilizes waste materials but also provides a viable source of functional elastin for biomaterial applications [159, 163].

1.8.5 Processes of Extraction of Elastin

Degumming

The extraction of elastin begins with the degumming of tissues to remove soluble proteins and lipids. This often involves washing the tissue in phosphate-buffered saline (PBS) or using alkaline treatments [159].

Chemical Hydrolysis

Elastin is typically solubilized by treating the tissue with sodium hydroxide or oxalic acid solution. Hot oxalic acid is particularly effective for breaking down cross-links in elastin fibers, thus aiding in its solubilization [164].

Filtration and Centrifugation

After chemical treatment, the solution undergoes filtration to separate insoluble materials from solubilized elastin. Centrifugation further assists in clarifying the solution and concentrating elastin [165].

Dialysis

The solubilized elastin solution is dialyzed against deionized water or buffer to remove residual chemical reagents and low-molecular-weight impurities [164].

1.8.6 Purification Techniques for Elastin

Desalting

Desalting can be performed using methods such as dialysis, ensuring a purified elastin preparation devoid of toxic residues [120].

Lyophilization

The purified elastin solution is often freeze-dried to obtain a stable powdered form. This step is crucial for long-term storage and simplifies logistics for later use [120].

Characterization

Techniques such as amino acid profiling ensure the integrity and purity of the extracted elastin, providing insights into its suitability for specific applications [159, 163].

1.9 Resilin

Resilin is a very elastic, proteinaceous biopolymer naturally found in insect cuticles, particularly at wing hinges and leg joints. It is renowned for its remarkable durability, flexibility, and capacity to endure repeated deformation without energy loss. Recombinant forms of resilin have gained attention for use in biomedical and soft tissue engineering applications due to their biocompatibility and mechanical durability [156, 166].

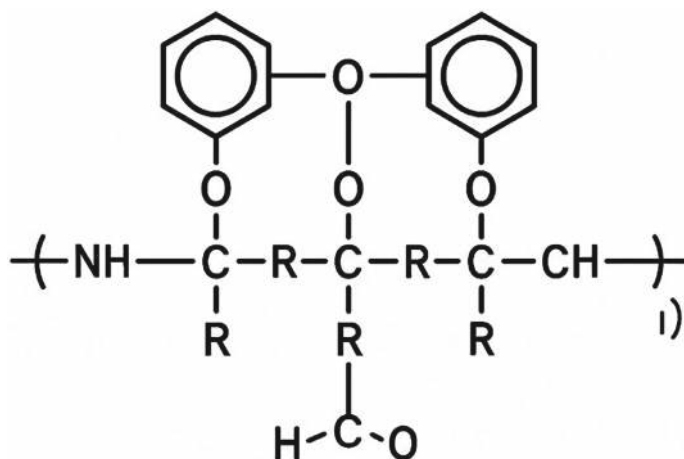


Fig. 9 A simplified, abstract diagram of the resilin polymer

1.9.1 Chemical Composition and Molecular Structure

Its molecular structure consists of repetitive sequences of mostly Glycine-Proline-X (where, X = often Tyrosine or Serine). The cross-links are formed by Dityrosine & trityrosine bonds that promote a random coil conformation, giving rise to its unique stretchability [156]. Resilin is particularly notable for its ability to recover its shape after substantial deformation with minimal energy loss, making it an excellent candidate for bioelastic materials [167, 168] (Fig. 9).

1.9.2 Physicochemical Properties

Solubility

Resilin exhibits limited solubility due to its extensive cross-linking in insect tissues but can be processed into soluble forms through appropriate polymerization techniques, creating materials with high elasticity [169].

Biodegradability

Resilin is biodegradable due its natural proteinaceous structure, allowing for gradual breakdown within biological systems, which is advantageous for temporary implants and tissue engineering matrices. The inherent biodegradability of resilin is favorable as it allows for the material to be replaced by newly formed tissues without accumulating harmful remnants in the body [156].

Mechanical Strength

Resilin exhibits one of the highest resilience levels in biological materials, supporting its function in insect joints and wings by minimizing energy loss during flexing [167].

Thermal Properties

Resilin demonstrated extensive flexibility and thermal stability, maintaining its mechanical properties over a wide temperature range [166].

1.9.3 Bioactivity

Biocompatibility

Resilin is a recognized for its remarkable elasticity and durability, predominantly located in insect cuticles (e.g., wing hinges, leg joints). Recombinant resilin-like polypeptides (RLPs) exhibit exceptional biocompatibility, demonstrating little cytotoxicity and promoting cell adhesion and proliferation, making them appropriate for tissue engineering, particularly in dynamic tissues such as cartilage and vocal folds [156].

Antimicrobial Properties

Native resilin do not have antimicrobial properties, however, few studies suggested that resilin could be engineered to include antimicrobial features when combined with antimicrobial agents or nanoparticles, enhancing their usability in applications such as wound healing and drug delivery systems [158].

1.9.4 Sources of Resilin

Insect Proteins: Resilin is primarily sourced from the cuticles of various insects, including those from the orders Lepidoptera (butterflies and moths) and Diptera (flies). It is characterized by its exceptional elasticity and is found in regions that require high elastic performance, such as tympanic membranes and wing joints [170, 171].

1.9.5 Processes of Extraction of Resilin

Solubilization

Resilin can be extracted by boiling insect cuticles in alkaline solutions, such as sodium hydroxide or urea, to break down protein structures and release the elastomeric protein [170].

Mechanical Treatment

A mechanical process may also be employed where insect cuticles are ground to enhance the efficiency of the chemical extraction, facilitating better solubilization of resilin [171].

Centrifugation

The resulting mixture from the extraction process is then centrifuged to separate insoluble materials, leaving a supernatant rich in solubilized resilin [172].

1.9.6 Purification Techniques for Resilin

Cold Coacervation

This method is often employed for the purification of resilin-like proteins. The cold-coacervation process uses temperature changes to induce phase separation, which allows for the isolation of resilin from other proteins [173].

Chromatography

Techniques such as size-exclusion chromatography can be utilized to separate resilin from contaminants based on molecular size, thereby purifying the protein for specific applications [173].

Electrospinning

Although not a purification method per se, electrospinning can be used to create nanofibers from solubilized resilin, thereby forming structures suitable for various biomedical applications [174].

Lyophilization

Similar to elastin, purified resilin can also be freeze-dried for storage and transport as a stable powder [173].

2 Conclusion

Animal-derived biopolymers provide a vital and adaptable class of naturally obtained materials with significant potential in medicinal, pharmacological, environmental, and industrial fields. Their remarkable biocompatibility, biodegradability, renewability, and mechanical integrity distinguish them as sustainable alternatives to petroleum-derived synthetic polymers. This chapter has provided an extensive analysis of several animal-derived biopolymers, including chitin, chitosan, collagen, gelatin, silk fibroin, keratin, elastin, resilin, and hyaluronic acid, emphasizing their chemical composition, physicochemical characteristics, origins, and developmental mechanisms.

From marine crustaceans and insects to livestock and poultry byproducts, the range of raw materials available for extracting these polymers highlights the value of utilizing biological waste in advancing a circular economy. Chitin and chitosan from crustacean shells, collagen and gelatin from bovine and porcine skin and bones, and keratin from feathers and hair are biodegradable and frequently derived from agro-industrial byproducts, highlighting their importance for both the environment and economy.

A prominent theme in the chapter has been the multifunctionality of polymeric polymers. In addition to their structural uses, they demonstrate bioactivity such as cell adhesion, tissue regeneration, and often possess antibacterial properties, either intrinsically or via functionalization. To mention a few are chitosan's antibacterial and film-forming attributes, collagen's scaffolding capabilities, gelatin's gel-forming abilities, and silk fibroin's mechanical strength facilitate their efficacy in tissue engineering, wound healing, drug delivery, and biodegradable packaging.

Significant advancements in extraction and purification methodologies have markedly enhanced the quality, safety, and efficacy of animal-derived biopolymers. Processes such as enzymatic deproteinization, mild acid hydrolysis, supercritical fluid extraction, and membrane-based purification have facilitated the generation of high-purity biomaterials that preserve their inherent biofunctionality. Furthermore, the advancement of recombinant analogues (such as resilin-like polypeptides and elastin-mimetic proteins) provide a novel approach to address sourcing and immunogenicity constraints while improving performance and scalability.

Despite their advantageous characteristics, numerous obstacles persist. Variability between batches, possible immunogenic reactions, ethical and religious considerations, and regulatory obstacles may restrict wider implementation. Moreover, in comparison to plant-based or microbial biopolymers, animal-derived biopolymers are comparatively under investigated, especially in specialized application domains.

Nonetheless, escalating investment in biomaterials research, coupled with advancements in biotechnological production processes, is progressively mitigating these issues.

The future combination of animal-derived biopolymers with nanotechnology, composite engineering, and functional biomolecules presents significant potential for the development of advanced materials. These innovations will probably extend their utility to intelligent drug delivery systems, antimicrobial implants, and three-dimensional bioprinting for regenerative medicine.

In conclusion, animal-derived biopolymers present an advantageous platform for the creation of environmentally sustainable, bioactive, and high-performance materials. With continued research, improved processing technologies, and growing environmental awareness, these biomaterials are poised to play a significant role in driving sustainable material science and shaping the future of biopolymer-based innovation.

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Chapter 3

Plant-Origin Biopolymers: Raw Material Sources to Their Development Process

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Abstract *Purpose:* This review chapter examines the development of plant-derived biopolymers as sustainable substitutes for petroleum-based plastics. In addition to discussing obstacles to their wider acceptance and industrial use, this study seeks to shed light on the origins of plant-based biopolymers, their development procedures, and current developments in the field. *Findings:* Biopolymers of plant origin

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are made from renewable resources, such as wood waste, starch, polyphenols, and agricultural waste. These materials have several advantages over traditional plastics, including biodegradable packaging, bio-reinforcements, and environmentally friendly substitutes. Inverse vulcanization, solvent-free polymerization, and enzymatic catalysis are advanced processing methods that have improved their mechanical and biodegradable qualities. Agricultural byproducts, such as plant proteins and triglycerides, aid in biomedicine, wound healing, and drug administration. The purification effectiveness, product recovery, and yield were enhanced via continuous chromatography, membrane systems, and microfluidics. These biopolymer qualities have been further improved for various applications by using nanofillers. **Summary:** Plant biopolymers are potentially renewable and sustainable alternatives to petroleum-based plastics. Developing high-performance materials and considerable improvements in processing methods have not eliminated problems with cost-effectiveness, scalability, safety, and allergenicity. Further research is essential to overcome these challenges and guarantee the broad use of plant biopolymers. The performance of these biopolymers can be enhanced by combining cutting-edge processing techniques with nanomaterials, strengthening their use in the manufacturing of sustainable products, and promoting a circular economy.

Keywords Biopolymers · Sustainable polymers · Renewable polymers · Green polymers · Plant-based polymers · Polysaccharides · Lignocellulosic · Life cycle assessment

Abbreviations

3D printing	3-Dimensional Printing
ASTM	American Society for Testing and Materials
ATPE	Aqueous Two-Phase Extraction
EOL	End-of-Life
FTIR	Fourier Transform Infrared
HPLC	High Performance Liquid Chromatography
LCA	Life Cycle Assessment
ML	Machine Learning
NMR	Nuclear Magnetic Resonance
PET	Polycarbonate Ethylene Terephthalate
PHAs	Polyhydroxyalkanoates
PLA	Polylactic Acid
PP	Polypropylene
R&D	Research and Development
TGS	Thermogravimetric Analysis
TPS	Thermoplastic Starch
UV	Ultraviolet

1 Introduction

The term “biopolymers” describes the macromolecules of monomeric units developed from biological sources, including plant, animal, and microbiological, formed through natural biological synthesis [1, 2]. Plant-based biopolymers are biodegradable and biocompatible, with a lower carbon footprint than petroleum-based polymers. Examples of biopolymers include cellulose, starch, lignin, and hemicellulose. Plant-based biopolymers are categorized into polyesters, lignin, polyisoprenes, polysaccharides, proteins, and polynucleotides. They are generally considered the most sustainable material for development. Biomaterials such as cellulose, starch, zein protein, and wheat gluten are widely used in food packaging, biomedical engineering, and agricultural production [3]. Recently, there has been an increase in acceptance and demand for plant-based biopolymers, with a projected market growth from 13.7 billion US dollars in 2021 to 35.25 billion US dollars by 2030, mostly in packaging, reinforcement, and biomedical fields [3], with Europe having the highest market share in 2023, driven by the growth of food and beverage, medical and healthcare, and other similar industries [4]. The summary of the 2023 global biopolymer market by region is presented in Fig. 1. The packaging segment held the highest market share with a cumulative annual growth rate of 10.4%, with polylactic acid, polyhydroxybutyrate as the major biopolymer materials [4].

According to Dutt and Sit [5], the wide acceptance of biopolymers, especially starch, cellulose, lignin, and protein, is due to their biodegradability and low environmental effect (low carbon footprints), therefore considered as the most sustainable

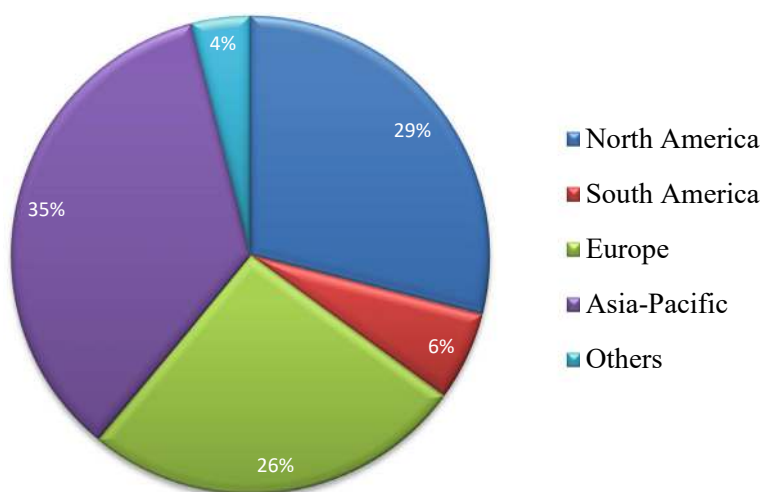


Fig. 1 Global biopolymer market by region for the year 2023. *Data Source* Analytic Research Consulting, [4]

material over petroleum-based plastics. These features of biopolymers are particularly important, especially in packaging and biomedical applications, where materials are required to exhibit specific behaviors that do not adversely affect the environment or the materials in contact [4]. However, challenges such as production cost, scalability, performance, and consumer acceptability limit the utilization of biopolymers. To address this, technologies such as compositing/blending, plasticizing, and nanoparticle reinforcement have been studied. Additionally, biopolymers show promise in active and intelligent packaging material systems, anti-microbial ability, sensor incorporation, shelf-life extension, and monitoring food quality over time.

In addition, biopolymers show more excellent functional characteristics, mechanical strength, and protection ability, giving them a cutting advantage over petroleum-based polymers, especially in packaging, automobiles, buildings, and biomedical applications [6], showing excellent natural degradation ability, offering insignificant or no environmental pollution [7, 8]. Plant-based biopolymers also show modification and compositing ability, extending their suitability and functionality [8, 9]. This chapter presents a comprehensive review of current research on bio-based polymers, including their raw materials and applications. It outlines the key challenges and future directions in the development and use of plant-derived biopolymers and provides a holistic comparison of plant-based biopolymers with synthetic or petroleum-based polymers.

2 Source of Plant-Based Biopolymers Raw Material

The most common sources of plant-based polymer raw materials are wood, plant parts, algae, seeds, and agricultural waste/byproducts (Fig. 3). These materials are primarily composed of polysaccharides (such as starch, cellulose, and pectin, Fig. 2) and are often biodegradable, non-toxic, and environmentally friendly for both the ecosystem and human health. Protein-based polymer raw materials, such as zein and soy protein, are also biocompatible and edible, demonstrating excellent barrier properties that make them suitable for packaging and drug delivery [9]. Lipid-based raw materials, including waxes and triglycerides, offer enhanced strength, flexibility, and water resistance. Lignin, on the other hand, contributes to carbon sequestration and structural stability. Polyphenol raw materials, such as tannins and flavonoids, exhibit antioxidant, antimicrobial, and UV-resistant properties, as well as medicinal benefits, making them ideal for functional coatings and packaging. Other plant-based materials, like natural rubber and latex, are biodegradable, providing greater elasticity and reducing dependence on fossil fuels. These polymers present an alternative to synthetic polymers, promoting sustainability, environmental safety, and industrial innovation.

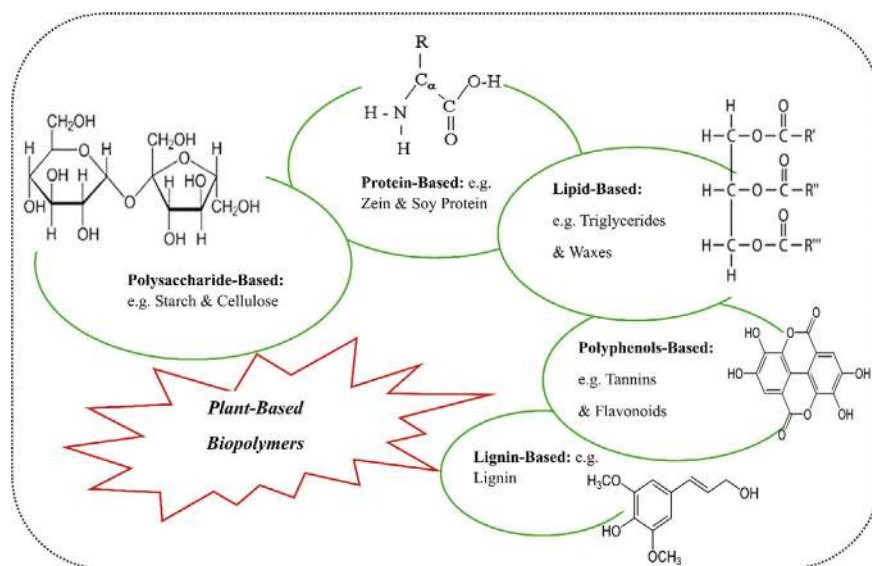


Fig. 2 Types, basic structures, and examples of plant-based biopolymers

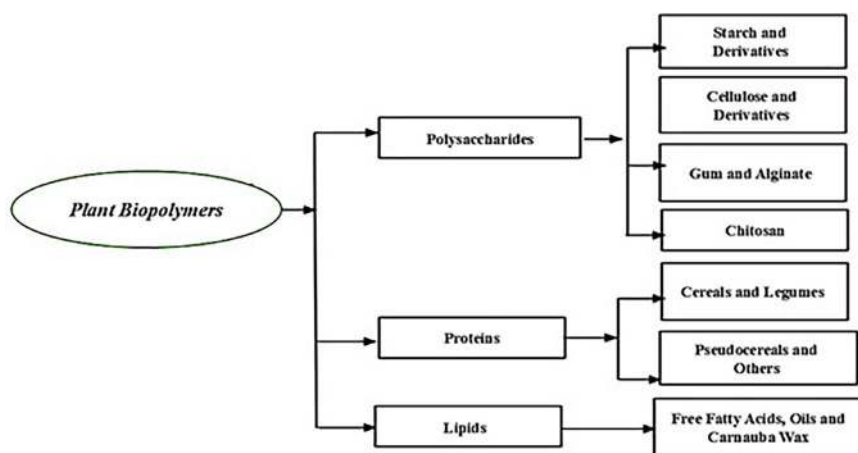


Fig. 3 Biopolymers raw materials

2.1 Polysaccharide Raw Materials

Polysaccharides are polymeric compounds consisting of a large group of sugar monomers. The most widely used raw material for biopolymer production of polysaccharide is starch. Starch is obtained from cereal crops, root and tubers, and legumes or food processing or agricultural biomass; the structure of starch (Fig. 4)

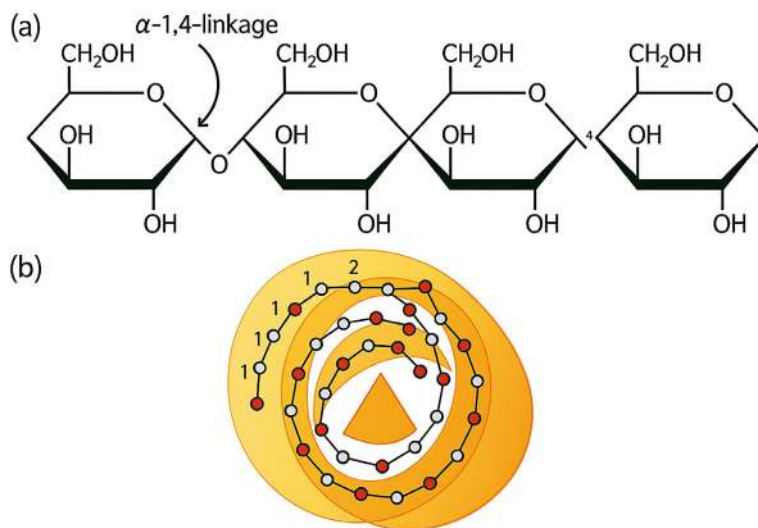


Fig. 4 **a** Joined units and **b** helical structure of starch

consists of repeated glucose monomers in the form of amylose and amylopectin, the amylose made up of linear polysaccharide consisting of D-glucose joined by the α -1,4-glycosidic bond and covers about 10–30% of the monomeric units of starch.

Amylopectin, on the other hand, is a branched-chain polysaccharide consisting of glucose units joined together by primarily α -1,4-glycosidic bonds and occasionally α -1,6-glycosidic bonds, which is responsible for the branching nature. A molecule of amylopectin consists of about 25–30 units of glucose and covers 70–90% of the total starch mass [10]. Amylose contributes to the film-foaming ability of starch, while amylopectin contributes to the brittleness.

Due to its renewability and modifiable properties, starch can be processed into various products as a raw material (Fig. 5). Starch biopolymers are used as bioethanol for food and fuel, as particulate filler and adhesives in the paper and textile industries, as well as packaging materials [10]. In the pharmaceutical and chemical industries, starch is used in 3D printing and drug delivery to specific body sites. In the food industry, it is used as a binder, starch hydrolysate for fermentation, and as a component in food product development.

Starch biopolymers are renewable, cost-effective, and inherently biodegradable and are used as packaging materials, in drug delivery, and as a stabilizing component of pharmaceuticals and nutraceuticals. The properties of starch-based biopolymers can be tailored to meet specific industrial uses [5, 11]. They are inherently elastic and can be transformed into thermoplastic materials through gelatinization, often in conjunction with glycerol, as biopolymers.

Cellulose, on the other hand, is a fibrous carbohydrate found in plant cell walls, accounting for over 50% of the carbon found in the vegetable kingdom. Cotton fibrils comprise approximately 95% cellulose, wood is composed of up to 50%

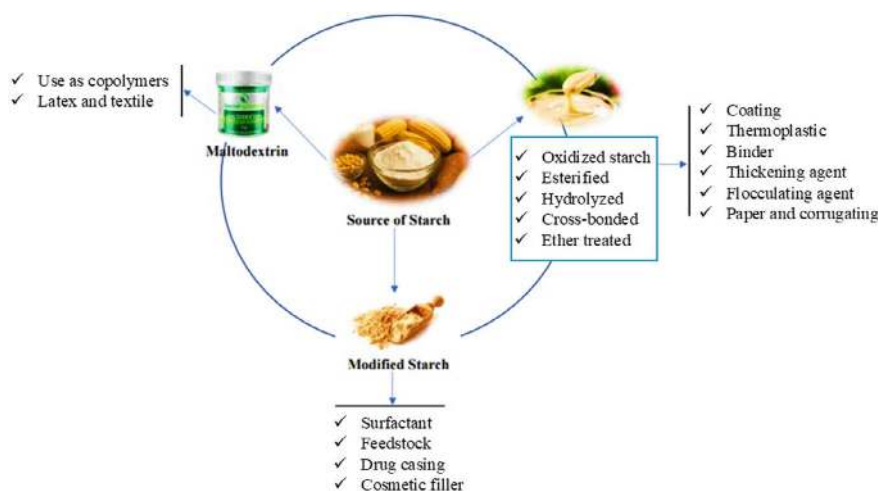


Fig. 5 Industrial uses and products of starch

cellulose, and dry-weight leaves contain about 10–20% cellulose. Cellulose, like starch, is composed of linear glucose monomers linked by β -1,4-glycosidic bonds, resulting in a more extended structure than amylose. This structure gives cellulose reduced solubility in water but excellent mechanical strength. Cellulose polymers have a helical structure and do not bind with coloring materials such as iodine. They are also indigestible to humans and require further treatment if used in edible packaging. Cellulose exhibits high thermal stability as a carrier for antioxidants and antibacterial agents, making it biocompatible and bio-composable. It can be used as a composite with other biopolymers, improving usability and renewability. Cellulosic biopolymers are generally non-corrosive, combustible, and non-toxic, with excellent supramolecular properties [12].

2.2 Protein-Based Biopolymer Raw Materials

Protein-based biopolymers are primarily derived from protein-rich foods, such as legumes (including soy, Bambara nut, and cowpea), cereals (like wheat), or pseudo-cereals. Other biopolymer materials are both economically viable and environmentally friendly and can also be obtained from renewable agro-industrial waste [13]. An example of a protein-based biopolymer is zein. Zein is a widely studied biocompatible and nontoxic protein-based biopolymer that has been used in biomedical applications [14]. Gelatin and whey protein have been used to produce biodegradable food packaging, providing excellent barriers to gas and sufficient mechanical properties [15].

2.3 Lipid-Based Biopolymer Raw Materials

Lipid-based biopolymer raw materials are plant-derived materials composed of triglycerides and waxes [5]. Lipid-based biopolymers possess excellent hydrophobic properties and heat stability, making them ideal materials for industrial applications. While the wax component provides a protective function, the triglyceride contributes to polymer formation by reacting with other monomers to impart polymeric properties. Lipid-based biopolymers are utilized as coatings, packaging materials, and biomedical applications, offering sustainability and biodegradability.

2.4 Lignin Raw Materials

Lignin raw materials are derived from lignocellulosic biomass from plants, which are generally environmentally friendly. Lignin is amorphous, consisting of aromatic phenylpropanoid monomers (Coumaric, coniferyl, and sinapyl alcohols). Lignin materials are used to produce phenolic resins, epoxy resins, and polyurethanes, usually through polymerization reactions. Lignin-based biopolymers require less energy for production compared with other plant-based biopolymers and have been tested for energy production, packaging, food formulation, and chemical synthesis [16]. Due to its complex structure and recalcitrant nature, lignin used in biopolymers has been challenging, requiring advanced processing techniques.

2.5 Polyphenol Biopolymer Raw Materials

Polyphenols are plant matter that have antioxidant, anti-inflammatory, and antimicrobial properties [17] and have been used in the development of value-added functional biopolymers [18]. Polyphenols interact with the protein component in plant-based biomass, providing structural and functional advantages that are beneficial in food packaging, biomedical applications, and environmental remediation. Polyphenolic compounds, such as catechins and gallic acid, stabilize gelatin-based films, enhancing their thermal and mechanical properties. The polyphenol component of pea protein gel enhances tea's rheological and digestive properties [19], providing better stability during processing and packaging. Besides being used in the food system, the advantages of polyphenols have also been utilized in the biomedical field, such as wound dressings and drug delivery, primarily due to their antimicrobial and antioxidant properties [20]. Bessa et al. [21] correlate the immune-modulating and anti-inflammatory properties of certain products used in drug delivery with their polyphenol content [22]. Polyphenol-based biopolymers have been developed as a composite product for water pollution remediation. Shah [23] also reported that polyphenol composite with fiber-reinforced biopolymer offers an alternative to

plastic. Aside from being naturally present in plant matter, polyphenol compounds can also be obtained from agricultural waste, such as grape pomace and sugarcane bagasse, thereby supporting green chemistry and the circular economy. These compounds can be processed into biodegradable materials, including packaging [24, 25].

2.6 Agricultural and Wood Waste Biopolymers

The impact of agricultural waste is primarily significant, particularly as it affects a substantial portion of our environment and climate. There is currently an effort to reduce agro-processing waste, particularly in utilizing it sustainably. Agricultural waste, such as sugarcane bagasse, wheat straw, rice husk, fruit peels, and other residues generated during post-harvest operations and industrial processing, is rich in polysaccharides, lignin, cellulose, and pectin, which, as previously discussed, are necessary raw materials for food, agriculture, materials science, and pharmaceutical science. Agricultural residue can be converted into high-value bioplastic with reduced environmental impact and carbon footprint [11]. The lignocellulosic monomers cover the vast portion of wood and can be processed into nanocellulose, such as nanofibrils and nanocrystals used as reinforcement material, offering both mechanical and structural properties with excellent crystallinity. The aromatic lignin component of wood can be valorized to improve the rigidity, UV stability, and antioxidant ability of biopolymer matrices [1].

2.7 Advantage of Plant-Based Biopolymers Over Conventional Fossil-Based Polymers

Aside from being easier to source, plant-based biopolymers are naturally biodegradable, meaning they can break down into harmless components, such as water, carbon dioxide, and decomposing biomass, thereby reducing environmental pollution [1, 11] caused by fossil-based plastics, including polypropylene. Plant-based biopolymers can also be engineered through simple to advanced methods to enhance their functionality while maintaining low or no toxicity. Plant-based biopolymers have a lower environmental footprint and reduce greenhouse gas emissions with a more sustainable lifecycle than conventional polymers. Plant-based biopolymers are primarily sourced from animal and plant biomass. In contrast, fossil-based polymers are obtained from natural sediments, such as crude oil, which requires deep excavation into the earth, is a high-energy source, and causes the release of toxic gases into the atmosphere. Research has shown continuous depletion of natural fossil sediment, which is often the source of conventional polymers, increasing their potential for extinction/exhaustion soon. However, biopolymers are as living as humans, usually sourced

from natural plant and animal residues, and can easily be regenerated into other valuable products. Therefore, development in biopolymers will reduce the dependence on fossil fuels and lower carbon emissions [26], reduce pollution [27], minimize waste and resource depletion, and improve the circular economy [28]. Compared to their counterparts, biopolymer products are often edible, with improved thermal and mechanical stability [29], high material performance [30], enhanced barrier properties [31], and better flexibility. A summary of the advantages of biopolymers is presented in Table 1.

3 Development and Processing Techniques of Plant-Based Biopolymers

In recent years, there has been growing interest in the development of suitable and sustainable processing techniques for plant-based biopolymers due to several factors, including their potential to replace conventional synthetic polymers, which are often non-biodegradable and can contribute to the overwhelming environmental pollution, advocacy campaigns on climate change also substantiate the demand for sustainability in the development of efficient processing technologies for plant-based biopolymers. In this section, the various techniques involved in developing and processing plant-based biopolymers will be highlighted to capture the extraction methods, production techniques, and their application, while also identifying the challenges and future directions.

Production of plant-based biopolymers has been achieved through both chemical, biological (microbiological), and physical methods, with microbial fermentation, chemical synthesis, and blending being the most promising techniques, attracting simplicity, cost-effectiveness, and suitability with the environment. Biodegradable polyhydroxyalkanoates (PHAs) have been produced through microbial fermentation by bacteria using carbon storage substrate, finally extracted through a green extraction technique [36]. In another process, polylactic acid (PLA) was derived from lactic acid through chemical synthesis of monomers via polymerization in a fermented plant-based feedstock. Blending in another way has been used to improve the mechanical and thermal properties of plant-based polymers by incorporating them with other natural or synthetic polymers. However, the processing methods for plant-based biopolymers have been further classified into two main categories: traditional and advanced processing methods.

In traditional methods, thermal processing and solvent-based polymerization technologies have been used to improve industrial quality, mechanical strength, solubility, and functionalization [13], usually in packaging applications, the biomedical field, and agriculture. However, traditional methods of biopolymer processing have been linked to high energy consumption, cost ineffectiveness, and hardship in solvent recovery. Advanced techniques for plant-based biopolymer production, such as inverse vulcanization (which involves using sulfur with plant-based compounds),

Table 1 Advantages of plant-based biopolymers over conventional synthetic polymers for sustainable application

Category	Examples	Sources	Applications	Advantages over synthetic polymers	References
Polysaccharide-based	Cellulose, starch, pectin, chitosan, alginate, carrageenan, guar and acacia gums	Wood, plants, algae, seeds	Packaging, biomedical, food, textiles	Biodegradable, renewable, non-toxic, compostable, reduces microplastic pollution	[5, 32]
Protein-based	Zein, wheat gluten, soy protein, casein, whey protein	Maize, wheat, soybeans, dairy	Films, coatings, drug delivery, tissue engineering	Edible, biodegradable, renewable, good barrier properties, biocompatible	[33, 34]
Lipid-based	Triglycerides, waxes, phospholipids, glycolipids	Vegetable oils, seeds, plant cuticles	Bio-based coatings, emulsifiers, food industry	Hydrophobic, biodegradable, renewable, improves material flexibility	[1]
Lignin-based	Lignin, lignocellulosic biomass	Wood, agricultural waste	Adhesives, biocomposites, biofuels	Abundant, biodegradable, high carbon content, enhances mechanical strength	[16]
Polyphenol-based	Tannins, flavonoids, phenolic acids	Bark, leaves, fruits, nuts	Antioxidants, functional coatings, packaging	Antioxidant, antimicrobial, UV-resistant, biodegradable	[35]
Other plant-derived polymers	Natural rubber, latex, resins, exudates	Rubber trees, plant resins	Biodegradable elastomers, adhesives, medical applications	Renewable, elastic, biodegradable, reduce dependency on fossil fuels	[35]

provide better thermal stability and mechanical strength [14]. However, there is still a need for research to evaluate and optimize these methods for better scalability and sustainability.

3.1 *Traditional Methods of Plant-Based Biopolymers Processing*

The increase in the adoption of traditional plant-based biopolymer processing has been linked to its environmental friendliness and sustainability over the petrochemical plastic, especially the biodegradability, which offers low or no carbon emission that can affect the climate. Biopolymers of plant origin, such as those from the genus *Cordia*, exhibit low toxicity and biocompatibility, making them ideal for various applications, including food, pharmaceuticals, and other biomedical uses. Traditional processing techniques, such as electrospinning, 3D printing, and solvent casting, have been integrated to enhance the quality of biopolymers and improve their suitability for packaging, biomedical applications, and scaffold engineering. According to Hussain et al. [37], the valorization of agro-food waste into biopolymers provides an innovative approach to reduce plastic pollution while utilizing abundant natural resources, which are often not regarded as useful. Therefore, integrating these valorized food waste as polymers into the packaging system, especially in the food and dairy sectors, underscores their potential to address plastic pollution while ensuring safety on land and sea. Also, according to Rizvi [38], the synthesis of plant biopolymers through traditional techniques offers a promising approach to sustainable material development. A major setback in using conventional methods for biopolymer production is their high-temperature requirements, which often lead to the denaturation or degradation of the monomers. Therefore, there is a need for precise temperature–time control to maintain the product’s functionality and integrity. Future research should aim to optimize processing conditions to achieve improved mechanical and biostability of biopolymers. Thermal treatment causes significant changes in the structural formation of biopolymers. Gelatinization in starch-based biopolymers improves their pasting capacity and gel strength.

3.1.1 Thermal Processing of Plant-Based Biopolymers

Thermal processing methods for plant-based biopolymers involve techniques that help modify the techno-functional properties of the polymer. During thermal processing, the biopolymer components are subjected to a controlled heat treatment that modifies their crystallinity and molecular structure. Thermal processing of starch-based biopolymers resulted in gelatinization, which influences the pasting capacity, gel strength, and water absorption capacity, making them the most suitable candidate in developing adhesives, coatings, and biodegradable films [1]. At elevated temperatures up to 80–100 °C, cellulose biopolymers were extracted from wood waste and other plant sources using a strong alkali solution that breaks down the lignin structure, making the lignin isolation simpler and more efficient. In combination with thermal treatment, microbial (bacteria) and chemical methods are also employed to improve the quality, efficiency, stability, and suitability of biopolymers, such as biodegradability. High-temperature cross-linkage of lignin enhances its mechanical

strength and thermal stability, making it a more suitable and more valuable component in biodegradable packaging material development. Despite these advantages, the thermal processing of plant biopolymers suffers from serious challenges, such as polymer degradation, especially at high temperatures or when temperature control is not precise. Future research should, therefore, focus on developing more optimized conditions, processes, and systems to ensure better retention of the mechanical and biodegradability of thermally treated plant-based biopolymers.

3.1.2 Solvent-Based Polymerization in the Processing of Plant-Based Biopolymers

Solvent-based polymerization has been used widely in synthesizing plant-derived biopolymers, especially polyphenol-based polymers, lignin, and hemicellulose materials. Solvent-based polymerization involves dissolving monomeric precursors in organic or aqueous solvents to speed up polymer chain formation. Research shows that solvent-based polymerization is effective, especially by its potential to improve polymer solubility, processing flexibility, and mechanical strength/stability modification. This makes it the most used method in coating biodegradable packaging, encapsulation of bioactive compounds, and in the production of bio-adhesives [1]. Despite its suitability and efficiency, solvent-based techniques require a large amount of chemical solvent for extraction, of which a large part cannot be efficiently recovered, reducing sustainability and environmental suitability. Several technologies have been developed to curtail this problem; Nuclear Magnetic Resonance (NMR) has been used to improve the scalability and efficiency of lignin polymerization, making it a more eco-friendly and biodegradable plastic substitute. Other techniques include whole-cell wall analysis. Solvent-based polymerization methods enable the production of high-molecular-weight biopolymers through ring-opening polymerization and condensation reaction, making them competitive methods, especially in the production of alternative polymers for petroleum-based polyesters [39].

3.2 Advanced Methods of Processing Plant-Based Biopolymers

Advanced methods of biopolymers processing have been developed due to their suitability in improving polymer properties above synthetic materials, especially in packaging development. Liang et al. [6] reported advanced extraction techniques of natural biopolymers such as cellulose, chitosan, and plant-based polysaccharides with excellent mechanical and biodegradability. New innovative processing techniques combined with suitable recipe formulation for biopolymers resulted in a final product with enhanced containment, mechanical, and other techno-functional properties compared to traditional plastics. Research shows that integrating proteomic and

metabolomic technologies helps identify biomolecules in biofilm material development, addressing the detrimental effects of food safety and preservation. Also, advanced analytical methods such as two-dimensional High-Performance Liquid Chromatography (HPLC) and size exclusion chromatography are used to characterize the complex structures of biopolymers to ensure that their properties meet or exceed their conventional counterparts [40].

3.2.1 Inverse Vulcanization of Plant-Based Biopolymers

Inverse vulcanization employs sulfur to generate a highly crosslinked polymer network from a low-value industrial byproduct of plant origin. During the vulcanization, the excess sulfur transformed into functional components of the polymer matrix, enhancing the biopolymer's resulting thermal and mechanical stability while maintaining the biodegradability. Polymers produced through inverse vulcanization enjoy a wide range of applications, including packaging, structural composites, and the biomedical field, with the high possibility of sustainability and performance. In another vulcanization method, elemental sulfur reacts with biobased compounds such as eugenol and magnolol to create an innovative biopolymer with promising multifunctionality. Shen [41] produced biobased polysulfide by reacting sulfur and eugenol. The biopolymer shows intrinsic flame retardance and excellent thermal remodeling capabilities, making it a great candidate in applications where safety and environmental sustainability are considered. Sulfur vulcanized biopolymers have been tested for catalytic application and show versatility above traditional petroleum-based polymers [34]. Also, through the vulcanization process, Jia et al. [42] highlighted the development of bio-based epoxy resin with reprocessing ability and biodegradability, indicating potential for recyclability and sustainability. Through inverse vulcanization, high-performing, eco-friendly polymers can be produced from plant-originating raw material.

3.2.2 Solvent-Free Polymerization of Plant-Based Biopolymers

No solvent is required to produce eco-friendly, efficient, and biodegradable packaging material in a solvent-free polymerization process. During the process, the thermal and mechanochemical conditions are controlled to induce direct polymerization without using a solvent mixture; therefore, the inefficiency of solvent extraction and environmental emission, and solvent waste effluent generation have been solved. Solvent-free polymerization has been used in processing sensitive feedstock such as cellulose and starch to maintain mechanical, biodegradability, and molecular integrity for final use as food packaging materials or as eco-friendly coatings. Deiana et al. [43] leverage the solvent-free technique to produce biobased hydrophobic coating through the enzymatic polymerization of ethylene brassylate using artificial cell walls. The final coating material shows high monomer conversion before final processing. Sarkar et al. [13] developed a novel green chemistry bioplastic

using water-insoluble plant protein without solvent or other cross-linkers. Plant oil-based polyester with high yield and excellent mechanical strength was produced by Zhang et al. [44], under a mild synthesis without solvent. In other instances, pectin-based polymer electrolytes for energy storage applications have been developed, highlighting the versatility of biopolymers in solvent-free processes [45]. Afewerki and Edlund [46] utilize the solvent-free polymerization technique to produce a curable biobased resin with mechanical and thermal properties that is also suitable for industrial applications.

3.2.3 Enzymatic Catalysis

This process appreciates mild operating conditions to push forward biocatalysis of plant-derived biopolymers using enzymes such as lipase and oxidoreductases, allowing the formation of a polymer with high stereospecificity under ambient temperature and near-neutral pH. Enzyme catalysis is an energy-conserving process that also obviates the need for chemical reagents, as such reducing the possibility of polymer degradation, improving efficiency, and resulting in biopolymer production with controlled molecular weights and tailored architecture. According to Ghatge et al. [39], the enzyme catalyst process is cost-effective and sustainable, especially due to its substrate-specific nature and its simplicity in the recovery of enzymes at the end of the process without generating harmful byproducts. In addition, the enzyme-catalyzed polymerization process can be combined with other conventional methods to offer a promising route for the production of high-molecular-weight biodegradable polymer with improved mechanical properties [1]. Biopolymers from enzyme-catalyzed processes are of superior quality in use, especially in drug delivery and tissue engineering, reinforcing their role as components in a sustainable circular economy.

3.3 *Purification Process of Plant-Based Biopolymers*

The quality, functionality, and safety of plant-based biopolymers as raw materials in food packaging, pharmaceuticals, drug delivery, and environmental remediation rely on their biodegradability and renewability, which is reportedly influenced by the efficiency of the purification process employed during their processing. The purification process of plant-based biopolymers involves the removal of impurities, non-reactive residue, and byproducts. The purification of biopolymers addresses the challenges related to cost, environment, and scalability. The process of biopolymers includes multiple steps, from enzymatic hydrolysis and filtration to precipitation. Enzymes such as pectinase and cellulase have been widely used to break down the cell wall and release biopolymers from plant biomass. The enzymes specifically target the cellular components without damaging the biopolymers and can be removed easily through conventional methods. The filtration steps in the purification involve

several techniques, such as suction filtration and centrifugation, to separate the rich biopolymer extract and residual solids. In contrast, the precipitation methods involve the flocculation of impurities by adding zinc sulfate or sodium hydroxide, which further purifies the polymers.

3.4 Extraction Techniques in Plant-Based Biopolymers Processing

The extraction process in biopolymers biopolymer processing consists of the advent of technologies in the recovery of biopolymer extracts, such as chitin, pectin, cellulose, and starch, from processing biomass. The most common methods of biopolymer extraction include both mechanical and chemical treatments, which, as such, require high energy intensity and may also generate harmful byproducts. To curtail this, researchers focused on bio-based techniques such as ionic liquids and deep eutectic solvents to extract biopolymers such as lignocellulosic materials from plant and food residues. The choice of these solvents was based on their extract selectivity and their ability to cause minimal environmental impact [47]. Other processes, such as microwave and ultrasonic-assisted extraction, have also been integrated to improve the efficiency and suitability of the extraction process [48]. Košťálová et al. [49] use microwave-assisted extraction to optimize pectin yield from pumpkin biomass using controlled heating time, temperature, and liquid-to-solid ratio combinations. Ultrasound-assisted and pressurized fluid extraction was utilized by Barão et al. [50] to improve process efficiency and reduce solvent and energy consumption. Venkatesan et al. [3] utilize the aqueous two-phase extraction (ATPE) technique to purify polyhydroxyalkanoates (PHAs) using thermos-separating polymers and salt, resulting in a scalable and cost-effective biopolymer for industrial use. The uses of these processes have also been linked to improving biopolymers' integrity, reducing solvent use, and also in the production of ideal polymers for food and medicinal use.

Enzyme and chemical flocculation have also been incorporated into biopolymer purification. Song et al. [51] removed protein impurities from polysaccharide extracts using a food-grade flocculant in chitosan, resulting in high purity and a minimal environmental footprint. Song et al. [51] utilized pH optimization for protein A coupling in affinity chromatography to improve the purity of monoclonal antibodies, resulting in a high recovery rate of excellent-grade purity biopolymer. Despite the efficiency of these purification technologies, the structural and functional characterization of biopolymers during the purification process has been challenging; however, the advent of advanced technologies such as Fourier Transformation Infrared (FTIR) spectroscopy and Thermogravimetric Analysis (TGA) has been used to evaluate molecular structure, thermal stability, and purity of isolated biopolymers [23]. The purification process of plant-based biopolymers is complex and multifaceted, requiring consideration of the extracts, the origin of the biomass, impurities, and characterization analysis.

4 Application of Plant-Based Biopolymers

The role of packaging material is to provide a total barrier to the external environment, i.e., provide containment, communication, and protection [52]. These properties are ideal for the functionality of bio-based polymer if used as a packaging material and in drug delivery. Recently, smart technology innovation has utilized plant-based biomass to produce packaging films that are both edible and biodegradable with excruciating functionality even above the conventional packaging. Edible packaging materials have been produced from plant-based materials such as protein and polysaccharides, which can be consumed with food. This new functionality resulted in higher acceptability of plant-based polymers [53], especially in the pharmaceutical, medical, and food industries. The use of edible polymer serves as an alternative to petroleum-based material, reducing cost, environmental impact, packaging waste, and pollution [54]. Additionally, they improve mechanical strength, flexibility, heat resistance, and antibacterial properties [55] and barrier qualities [56], as summarized in Fig. 6 (Table 2).

4.1 Application of Plant-Based Biopolymers in Food and Packaging Industries

Beyond packaging, biopolymers are widely employed as emulsifiers, thickening agents, and moisture retainers to enhance the stability and physicochemical characteristics of food emulsions (Table 3) [57, 58]. They also play a critical role in delivering bioactive compounds such as probiotics, which are sensitive to degradation during processing, storage, or exposure to harsh gastrointestinal conditions. In

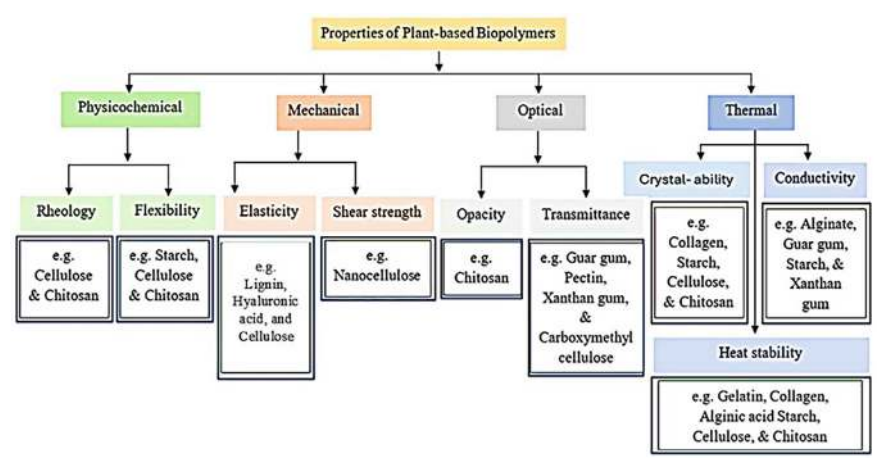


Fig. 6 Properties and examples of plant-based biopolymers

Table 2 Plant-based biopolymers in food systems

Biopolymer	Properties	Application	References
Agar	Swelling agent	Processed meat products	[59]
Alginate	Gelling agent	Milk-based dessert, jellies	[1]
Carboxymethyl-cellulose	Coating, emulsifying agent	Confectioneries, salad dressing	[60]
Gellan	Inhibitor	Frozen foods, sugar syrup	[61]
Guar gum	Thickening agent, stabilizer, gelling, emulsifier	Jam, syrups, pie fillings, fat replacer, coating for meat	[62]
Gum karaya	Syneresis inhibitor	Cheese, frozen foods	[63]
Hemicellulose	Binder	Pet foods	[56]
Pectin	Adhesive	Glazes and icing	[64]
Pullulan	Film-forming agent	Protective coating	[11]
Starch	Stabilizer, thickener	Ice creams, salad dressing, confectioneries	[65]
Xanthan gum	Foam stabilizer	Beer	[63]

the pharmaceutical sector, biopolymers have been utilized as drug delivery systems to enhance the stability and bioavailability of medications. Modified starch is used in bakeries, noodles, and confectioneries to enhance volume, delay staling, act as a filler, boost fiber content, and improve techno-functional properties [1]. Guar gum-based biopolymers serve as thickeners, foam stabilizers, gelling agents, emulsifiers, and anti-staling agents, with applications in beverages and fruit juices due to their excellent viscosity and water retention (added at 0.1–0.75%). Guar gum is also used in flavor encapsulation. Chitosan, obtained from crustacean shells, mollusks, insects, and fungi, is employed in antimicrobial biodegradable packaging films due to its biodegradability, antioxidant, biocompatible, and non-toxic properties (Fig. 7).

4.2 Biomedical and Pharmaceutical Applications of Plant-Based Biopolymers

In the biomedical sector, packaging is a technique that enables a pharmaceutical product to be closed from the point of manufacture to the point of usage. Biopolymers are utilized in pharmaceutical packaging to safeguard medications, surgical instruments, liquids, powders, pills, and nutraceuticals. Pharmaceutical packaging affects product isolation and guarantees product safety, identity, and usability. Packaging should be healthy for the environment, in line with the patient's condition, and not have any adverse health impacts. Encapsulation technologies have been used in pharmaceutical industries to utilize the flexibility of biopolymers to improve the

Table 3 Biopolymers used in pharmaceutical and biomedical encapsulation

Biopolymer	Encapsulated strain/ particle	Encapsulation method	Benefit	Source
Gelatin and chitosan agar	<i>Lactiplantibacillus plantarum</i>	Emulsification	Cellular viability, improved solubility	[72]
Alginate and chitosan	Vaccine with <i>Lactiplantibacillus plantarum</i>	Extrusion	Vaccine effectiveness and stability (>56 days)	[42]
	<i>Pediococcus acidilactici</i>	Extrusion	Cellular viability and release	[73]
	<i>Bifidobacterium breve</i>	Extrusion	Cellular viability up to 2 h in pH 2–5. Improve the stability of the capsule	[74]
	<i>Limosilactobacillus reuteri</i> DSM 17938	Vibration technology	Resistance to gastrointestinal stress	[75]
	<i>Saccharomyces boulardii</i>	Extrusion	Cellular viability and maintenance up to 6 h of administration	[76]
	<i>Lactobacillus acidophilus</i> and <i>Lacticaseibacillus casei</i>	Extrusion	Cellular viability	[77]
	<i>Bacillus amyloliquefaciens</i> , <i>Bacillus methylotrophicus</i> , and <i>Bacillus subtilis</i>	Vibration and extrusion	Capsule integrity and strain viability	[53]
	<i>Limosilactobacillus reuteri</i>	Emulsification	Cellular viability	[78]
Chitosan and hydrochloride alginate	<i>Bacillus licheniformis</i>	Orifice-polymerization	Microcapsule protection and improved cellular released	[78]
Alginate and gelatin	<i>Lacticaseibacillus rhamnosus</i>	Extrusion	Cellular protection	[79]
Alginate	<i>Lactococcus lactis</i> spp. <i>cremoris</i>	Extrusion	Cellular protection and drug delivery	[80]
	<i>Bifidobacterium pseudocatenulatum</i>	Extrusion	Cellular protection	[81]

(continued)

Table 3 (continued)

Biopolymer	Encapsulated strain/ particle	Encapsulation method	Benefit	Source
	<i>Staphylococcus succinus</i> and <i>Enterococcus</i> <i>faecium</i>	Extrusion	Cellular viability (up to 98.75%)	[82]
Alginate and milk	<i>Lactobacillus bulgaricus</i>	Extrusion	Viability and probiotic shelf life	[83]
Alginate and starch	<i>Limosilactobacillus</i> <i>fermentum</i>	Lyophilization	Stability and protection of probiotics in microparticle films	[78]
Alginate, chitosan, and locust bean	<i>Lactocaseibacillus</i> <i>rhamnosus</i>	Freeze-drying	Stress tolerance ($\times 6$), thermotolerance ($\times 100$), acid tolerance ($\times 10$)	[84]
	<i>Saccharomyces</i> <i>cerevisiae</i>	Emulsification	Higher stability and improved growth medium	[85]
Alginate and chitosan	<i>Bifidobacterium</i> <i>pseudocatenulatan</i>			[51]
	<i>Bifidobacterium breve</i>	Layer-to-layer	Layer matrix stability and strain gradually released	[86]
Alginate, starch, and chitosan	<i>Lactobacillus</i> <i>acidophilus</i>	Extrusion	Probiotic stability, storage ability	[87]
Alginate, chitosan, and xanthan gum	<i>Lactiplantibacillus</i> <i>plantarum</i>	Extrusion	Storage stability and cellular viability	

delivery, viability, release, and storage of viable antibiotics and probiotics. Encapsulated probiotics have also been incorporated into food products, including cheeses [66], yogurt, frozen dairy desserts, beverages [67], and meat products, improving their therapy as well as functional properties [68]. Biopolymer shows high protection of probiotics, sustaining their viability up to months under monitored conditions [69]. According to Baranwal et al. [1] encapsulation using biopolymers is achieved using the following technologies.

Extrusion: Extrusion technology has been used to produce food and pharmaceutical products with different techno-functional and physical properties. Extrusion encapsulation involves hydrocolloid formation followed by subsequent addition of the microorganism, probiotic, or nutraceutical to form a droplet through a preformed

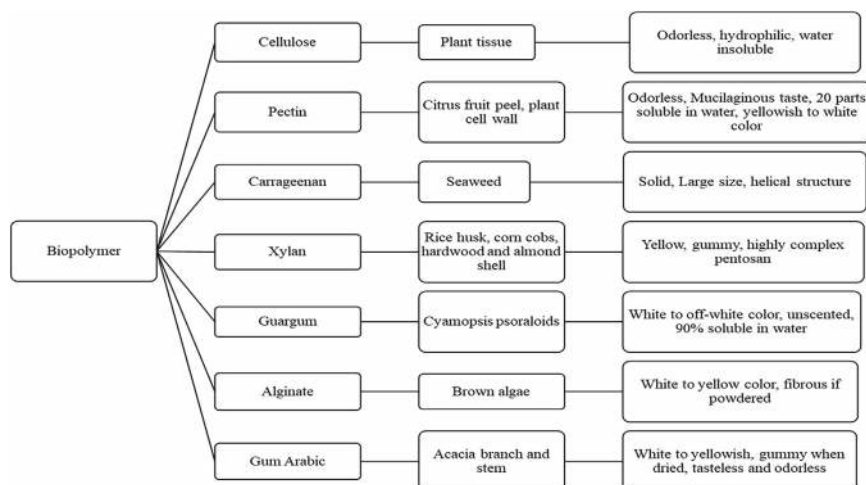


Fig. 7 Plant-based biopolymers, their sources, and properties

nozzle or piloted syringe, and their hardening into a final shape by releasing them into a hardening solution, mostly calcium chloride.

Emulsification: This is when a small volume of hydrocolloid suspension containing the encapsulation material is added to a more extensive phase (mostly vegetable oils) and the mixture is homogenized using a homogenizer. The emulsion is then insolubilized into a gel capsule, usually of varying sizes and shapes.

Lyophilization: This involves freezing the encapsulation material, including the organisms, to a temperature of -50 to 30°C . The stability of the lipolyzed product is improved by the addition of cryoprotectants such as milk, protein, trehalose, sorbitol, sucrose, and lactose.

Spray-Drying Method: This involves atomization of the encapsulated mixture, followed by evaporation with contact with hot air or gas at a controlled speed in a covered container to produce a relatively similar-sized capsule.

Microencapsulation: This technology traps an active agent in a coating material, preserving viability and protecting against odd environmental conditions. Through microencapsulation, the product is usually thin and strong, semi-permeable up to nanometers to millimeters in diameter.

Layer-by-Layer Technology: This technology involves the alternate coating of cationic and anionic biopolymers, such as chitosan and alginate, respectively, on cell surfaces through electrostatic interactions, forming stable multilayered structures for enhanced protection and functionality.

Spray-Freeze-Drying: This involves a combination of several technologies, including lyophilization and spray drying. Spray-freeze-drying provides a solution to size irregularity in spray-drying technology, but it costs more, requires a longer time, and uses more energy.

Recently biopolymer composites (Table 4) have been prepared using different technologies such as extrusion, grafting, electrospinning, solvent casting, molding, melt blending, film stacking, phase separation, intercalation, laser printing, and filament winding as well as mathematical modeling and used to employ the best techno-functional qualities of the polymers against environmental stress, storage, handling, and other specific production requirements [53]. Table 3 shows an example of biopolymers used in pharmaceutical encapsulation. Biopolymers have served as effective stabilizing agents for synthesizing silver nanoparticles [1, 70]. Through polymer-assisted synthesis, these approaches improve the polymer matrix, which improves rigidity and stability in the nanocomposite film. This approach can also have the potential to improve the antibacterial characteristics of non-composite [3, 71], improving film-forming, physical, and functional characteristics [71].

Table 4 Biopolymer composite in biomedical and pharmaceutical industries

Biopolymer	Encapsulated particle	Benefits	Application	Reference
Corn starch	Chlorhexidine gluconate	Steady delivery of the drug in vitro up to 21 days	Long-term drug delivery	[88]
	Clonidine	Improve delivery rate up to 30 μg in 15 min	Transdermal patches	[89]
	Salicylic acid	Diffusible delivery of drug to the cell membrane up to $4.11 \times 10^{-6} \text{ cm}^2/\text{s}$	Hydrogel membrane	[90]
Corn starch—ethylene vinyl alcohol mixture	Non-steroid anti-inflammatory	Immediate, slow, and controlled delivery of the drug up to 10 days	Drug delivery carriers	[91]
Potato starch	Ibuprofen, benzocaine, and sulphapyridine	Stable carrier ready for fermentation in the colon	Stable carrier	[92]
Glutinous rice starch, sodium alginate, and CaCl_2	Metformin hydrochloride	Speed up entrapment with higher solubility during delivery	Controlled drug delivery	[93]

(continued)

Table 4 (continued)

Biopolymer	Encapsulated particle	Benefits	Application	Reference
<i>Ensete ventricosum</i> starch	Epichlorohydrin	Stable delivery with improved burst release for up to 12 h	Drug-release sustaining pharmaceutical excipient	[94]
Starch-clay composite	Tramadol	Controlled drugs are released up to 350 min	Tablet formulation	[95]
Starch-chitosan	Hydroxyurea	Toxicity effects up to cancer-killing concentration	Cancer therapy	[78]
Corn starch-sponge matrix	Uranine, indomethacin, and nifedipine	Improved plasma capsule released up to 2.5%	Sustained capsule release	[96]
Starch-poly- β -caprolactone	Dexamethasone	Quick drug delivery and sustained drug release up to 30 days	Drug delivery and tissue engineering	[97]
High-amylose starch-microcrystalline cellulose	Ranitidine hydrochloride	Higher drug buoyancy with improved release up to 45.87% for sustained 10 h	Gastric-floating drug delivery system	[98]
	Probiotic	Better probiotic stability in acidic pH with higher cellular viability	Microencapsulation of probiotics	[99]
Chitosan	Acyclovir	Higher grafting efficiency up to 94% with slow drug release for 12 h	Drug delivery	[100]

(continued)

Table 4 (continued)

Biopolymer	Encapsulated particle	Benefits	Application	Reference
	Chlorhexidine diacetate	Improved tablet solubility and antimicrobial activity	Buccal tablets	[101]
Chitosan aspartate, glutamate, and hydrochloride	Vancomycin	Improved solubility in the upper gastrointestinal tract with sustained microspheric release	Peptide-based model drug	[102]
Chitosan	Tetracycline	Regulated drug delivery	Controlled drug system	[103]
Alginate	Rifampicin	pH-sensitive drug delivery up to pH 7.4	Drug delivery carriers	[104]
	Ibuprofen	Drug delivery up to 4 h	Drug delivery	[78]
	Metformin hydrochloride	Controlled delivery for diabetes	Drug delivery	[105]
	Diclofenac sodium	Controlled delivery even at higher polymer ratios up to 1:3	Controlled drug released	[106]
	Nicotinic acid	Drug delivery is released up to 4 h	Aerogels	[107]
	Furosemide	Intestinal drug delivery	Controlled drug delivery beads	[82]
Alginate and methylcellulose	Indomethacin	Controlled drug delivery	Drug delivery	[108]
Alginate and sodium carboxymethylcellulose	Ceftriaxone sodium	Improved diffusible drug delivery at different pH	Multi-articulated beads	[90]
Alginate, carboxymethylcellulose, and chitosan	Amoxicillin	Prolonged drug released up to 8 h at gastric pH	Coated beads	[78]

5 Challenges in Scaling and Adoption of Plant-Based Biopolymers

The most important properties of plant-based biopolymers are their sustainability in terms of renewability, biodegradability, and lower environmental impact than conventional petroleum-based polymers [109], making them the ideal candidate for the packaging, automobile, and biomedical industries, reducing pollution and carbon footprint [7, 110] with excellent modifiable and composite forming ability [8, 9]. Despite their advantages and sustainability in industrial applications, the adoption, large-scale production cost, and availability of technologies hinder the maximum utilization of plant-based biopolymers' functionalities. Some plant-based biopolymers are reported to have poor mechanical strength, durability, and thermal suitability, necessitating further research and development. Also, according to Sukumaran and Jano [8], the inefficiencies in biopolymer processing require the development of cost-effective technologies that will still maintain the inherent quality of the biopolymers. Discussions in this section are the significant challenges impeding the scale-up and adoption of plant-based biopolymers.

5.1 Production Challenges in Scaling Biopolymers Production

Most of the challenges in biopolymer production aim to address the economic viability and achieve a competitive advantage over conventional processing methods. Heat treatment during the production of heat-sensitive biopolymers, such as starch, chitin, and cellulose, limits scalability. Therefore, the advent of low-temperature or solution-based technologies, which are often costly and environmentally unfriendly, is currently in use. To bridge this challenge, there is a need for new technologies that will maintain the polymer's efficiency and give sufficient investment return [111]. The variability of raw material (plant inputs) affects the final mechanical and other techno-functional attributes of final plant polymers [110]. The advent of genetic engineering is therefore required to address the concentration variability and offer uniformity for a better quality and regulatory compliance. There is a need for a standard biodegradability testing system and environmental impact assessment, such as energy-intensive plasma treatment, maybe through Life Cycle Assessment (LCA), to identify and mitigate environmental hotspots [112, 113].

5.2 *Economic and Market Challenges*

Economic challenges, including high production costs, limited technology scale-up, funding constraints, and consumer acceptance issues, significantly impact the adoption of technologies and products derived from plant-based biopolymers. Although the cost of carbon-based monomers is higher than that of petroleum-derived ones, the use of agricultural byproducts as substrates has been linked to improving the economic viability of plant-based biopolymers [114]. New technology innovations, such as combining polylactic acid (PLA) and thermoplastic starch (TPS), have been utilized to produce cost-effective multilayer biopolymers [112]. Albadran et al. [72] reported that small-scale production of biopolymers and the inexpensiveness of raw materials stock make them more economically competitive than synthetic polymers; therefore, the need for upscaling technologies for higher scale production is paramount in improving economy and profitability in biopolymer production [115].

Currently, most biopolymer production industries are either start-ups or small-scale, lacking the high capital required for growth and development. The initial high investment cost for biopolymer products has also been a bottleneck for investors. Therefore, there is a need for financial incentives and funding mechanisms, such as micro-scheme loans, to support biopolymer startups and encourage investment [115, 116]. The consumer awareness campaign is also required to enable sustainability and public consumption, which in turn improves business return; therefore, there is a need for wide consumer education regarding the benefits, suitability, safety, and performance of biopolymers to improve their acceptance and drive demand for profit [117, 118].

In another turn, the acceptance of biopolymers is negatively driven by misconception and misinformation, especially regarding performance, durability, and quality, which affects consumer acceptance [117, 119]. Many consumers believe that biopolymers, including polylactic acid and starch-based plastic, are inherently weak and less durable than petroleum-based plastic, such as polypropylene (PP). This misconception mostly arises from early-generation biopolymers, which were produced (due to a lack of sufficient technologies) with low mechanical strength and thermal stability [120]. Therefore, addressing misconceptions, misrepresentations, and misinformation on plant-based biopolymers through effective marketing and communication strategies could boost customers' confidence and engagement in biopolymer products [117, 119].

5.3 *Regulatory and Policy Constraints*

Inconsistent standards and requirements for certification, international trade barriers, and a lack of uniform global trade practices impede the production level of plant-based polymers [2, 121, 122]. Even though the certification process for biopolymers is evolving, the testing methods are often inconsistent with regional differences [2,

[121]. This regionalism in standard and certification requirements policies is exacerbated due to the lack of globally harmonized policies, making it difficult for production companies to navigate the regulatory landscape in full [122, 123]. Even in the developed world, a lack of uniformity persists among governments. The European Union follows the EN 13432 certification, focusing on biodegradability and compostability criteria, which differ from the ASTM D6400 standard in the United States. These political disparities hinder the cross-border compliance and acceptance of biopolymer products [123], with consumers limited to only local products, even if they do not meet their process or quality requirements.

Although biodegradability tests in biopolymers are important, the lack of standardized criteria and testing methods makes it difficult for organizations to adopt, maybe due to the variations that exist between laboratories, which further complicate the certification process [2, 121]. Furthermore, [124] opined that composting facilities are often reluctant to accept certified biodegradable/compostable products due to existing variability in the product disintegration rates and specific composting condition requirements. This underscores the complexities and challenges in biopolymer certification and processing and highlights the need for harmonized standards and testing methodologies.

Other challenges include a lack of government support, such as funding for research and development, hindering the research and production of technologies, testing procedures, as well as harmonization of standards. In Canada alone, there exist varying policies between provinces, which complicate compliance, while in developing worlds such as Nigeria, these policies/government supports are often non-existent, with zero or very limited support for production [26]. Therefore, the development of biopolymer production relies on government backing, globalized standards, innovative R&D, and strong, harmonized government policies that will drive growth and innovation.

5.4 *Challenges of Environment and Sustainability*

The environmental challenges for full-scale biopolymer production are already significant, including concerns about the negative impacts of industrial agriculture on the environment, such as competition with food production, water use and quality issues, biodiversity loss, and inadequate waste management. There has been an expectation of exacerbated food insecurity and environmental degradation due to the expansion of large-scale agriculture to promote the production of bio-raw materials for biopolymer production. This competition between large-scale agriculture production and biopolymers may increase habitat fragmentation, greenhouse gas emissions, and soil erosion [125], negating sustainable development. For example, Rulli et al. [126], postulated that if biofuels occupy 4% of global arable land and use 3% of global agricultural water resources, it will only potentially feed 30% of the malnourished world population, which will possibly escalate hunger and insecurity therefore,

sustainable land practice will be required at intensive rate including optimized fertilizer use, improved crop diversity, and climate-smart agricultural technology. These intense practices on land will lead to environmental damage necessitating sustainable agricultural practices and resources conservation [125]. Even though biopolymers are biodegradable, their end-of-life remains unknown [127, 128], although they might be recyclable, the cost of recycling and waste management infrastructure escalate environmental effects [129, 130]; therefore, advancing waste management and biotechnological recycling including bio-upcycling, could improve circular economy for biopolymers [131, 132].

Another challenge in scaling production and adopting plant-based biopolymers is the compounding issue of carbon footprint, which is linked to the environment, and energy efficiency, often assessed through the LCA methods [133, 134]. The LCA identifies the stage in the biopolymers' life cycle that contributes the most to their environmental impact, enabling targeted improvements to reduce emissions [133, 134]. LCA studies on diapers composed of biopolymer composites, including PLA, as reported by Mirabella et al. [135], revealed that the initial raw material source (pulp) and the sodium polyacrylate components had a significant environmental impact, while energy consumption was relatively low. This agrees with Gironi et al. [136], who opined that PLA has higher human health, resource-intensive cultivation, and ecosystem impact compared with PET bottles despite its renewable origin. Shen [41] asserts that bioplastic materials can reduce fossil fuel dependence but have significant land and water impact that will interfere with global food security and earth biodiversity; therefore, there is a need for a comprehensive LCA assessment for each bioplastic material developed before certification and or patenting. The LCA will provide a comprehensive perspective that balances trade-offs and guides decision-making toward more sustainable options [134, 137]. Although the challenges of biopolymers adoption and production are still under study, Table 5 provides the most important and reported challenges hindering the production and adoption of plant-based biopolymers.

6 Conclusion and Future Prospects

Plant-based biopolymers have shown a promising raw material and production perspective with their products being more environmentally friendly, with low greenhouse gas emissions, high biodegradability, low pollution potential, simplicity, and potentiality for use in many fields across agriculture, packaging, food production, pharmaceutical, and biomedical fields, offering both sustainability, economic advantage, competitiveness, technical limitation, and low regulatory barriers more than conventional fossil-based polymers. The monomers of biopolymers exhibit innovative functionality, including suitable mechanical, moldability, thermal, and other techno-functional properties. Despite their advantages, the production and technology scale-up of plant-based biopolymers face challenges, including limited standards for testing, a lack of globally harmonized standards for testing and certification,

Table 5 Challenges and solutions in scaling and adopting plant-based biopolymers

Category	Challenges	Suggested solutions	References
Technical challenges	Inefficient processing techniques	Develop novel thermal processing and fibrillation approaches	[110, 111, 113]
	Variability in raw material quality	Standardization of raw material selection and production methods	
	Low production yields from natural sources	Genetic modification of the polymer sources to improve yield and polymer content	
	High energy requirements for some processes	Optimization of processing conditions and integration of energy-efficient methods for processing	
Economic and market barriers	High production costs compared to petroleum-based plastics	Scale up production and use cost-effective raw materials	[116, 118, 138]
	Low economy scale-up	Automation to facilitate large-scale production	
	Low investment and funding for R&D	Increase government-private partnerships that facilitate funding for R&D	
	Consumer misconceptions and low awareness	Launch educational campaigns and transparent labeling	
Regulatory and policy issues	Inconsistent biodegradability and compostability standards	Establish a globally harmonized standard and certification requirements	[2, 121, 122, 139]
	Complex international trade regulations	Streamline regulations through global policy collaboration	
	Difficult certification and compliance processes	Develop clear, standardized certification procedures	
	Low government commitment to incentives	Reduced tax, increased grant, and micro-scheme loans for production	

(continued)

Table 5 (continued)

Category	Challenges	Suggested solutions	References
Environmental and sustainability concerns	Competition with food production for agricultural resources	Focus on non-food raw materials, Agro-products, and waste	[127, 128, 132, 137]
	The high environmental footprint of large-scale farming	Promote sustainable farming and land-use practices	
	Limited end-of-life (EOL) solutions and waste management infrastructure	Expand composting, recycling, and bio-upcycling facilities	
	Disposal and recycling issues	Innovative formulation that focuses on biodegradability and low environmental impact	

cross-border barriers due to differences in regulatory and compliance requirements, the sustainability of raw materials, consumer education, and the adoption of sustainable practices. Despite setbacks, the global acceptability of plant-based biopolymers is on the rise, driven by a continuous demand for cost and eco-friendliness.

At the phase of global innovation, the future of biopolymers is promising, driven by its production simplicity, innovation, collaboration, and policy support to enhance sustainability by reducing the compounding social and environmental effects of synthetic plastic. Researchers are now focusing on improving the functionality and performance of biopolymers through advanced processing technologies, including machine learning and polymeric nano-formulation; therefore, future research should demonstrate sustainability through advanced shelf-life testing, LCA, and harmonized testing methodologies to enable global adoption. Integrating bio-raw materials has been applied in almost all aspects of human development, cutting across agriculture, food, pharmaceutical, and medicine. Plant fiber has been integrated to accelerate biodegradation in PLA composite, while refined bio-composites have been in production, which shows promising compatibility for 3D printing. In agriculture, crop yield has been improving through nano-fertilizer formulated with polysaccharide-based nanoparticles. Circular economy models have also been developed to enhance the scalability and mechanical strength of agro-based biopolymers. The future of plant-based biopolymers, although promising, may be hindered by production costs, scalability, and mechanical performance issues. However, with the advent of policy reforms, collaborative R&D, harmonized standards, and interdisciplinary collaboration, the potential of biopolymers can be unlocked to its fullest, thereby improving sustainability and environmental benefits. The emerging trends and the challenges in plant-based biopolymer development are highlighted in Table 6.

Table 6 Emerging trends and challenges in plant-based biopolymer innovations

Category	Prospects	Advancements and benefits	Challenges and considerations	References
Machine Learning (ML) in biopolymer processing	Optimization of biopolymer production processes through ML-based data analysis	Improved efficiency, enhanced product quality, and predictive modelling for process control	Data availability, computational cost, and integration with existing systems	[114]
Biopolymer applications in packaging	Development of green biopolymers with improved mechanical and barrier properties	Sustainable alternatives to plastics enhance durability and reduce environmental impact	Cost-effectiveness, large-scale production challenges, and regulatory compliance	[140]
Nano-formulations for bioactive delivery	Use of nanoencapsulation and stimuli-responsive systems in agriculture	Targeted delivery, increased bioavailability of plant bioactive compounds, and improved crop protection	Scalability, cost-effectiveness, and potential environmental concerns	[141]
PLA composites with plant fibers	Incorporation of plant fibers to accelerate PLA biodegradation	Enhanced biodegradability, a sustainable alternative to traditional plastics	Processing challenges, mechanical property optimization	[142]
3D printing with PLA biocomposite	Optimization of material properties and processing parameters for additive manufacturing	Improved mechanical performance, customization potential, and reduced waste	Compatibility with 3D printing technologies and the cost of materials	[143]
Nanotechnology in agriculture	Advanced nanoencapsulation for nutrient delivery and stress tolerance in crops	Enhanced stability, bioavailability, and eco-friendly crop management	Regulatory concerns, safety assessments, and large-scale implementation	[141]
Polysaccharide-based nanoparticles	Encapsulation of eco-friendly compounds for controlled release	Biodegradability, reduced chemical inputs in agriculture	Production costs and potential toxicity studies are needed	[144]
Nano-biofertilizers	Biopolymer-based nano-fertilizers to improve soil quality and crop yield	Reduced environmental impact, improved efficiency of nutrient absorption	Stability during storage and transport, and cost constraints	[145]
Integration of biopolymers with metallic nanoparticles	Development of multifunctional materials for agricultural applications	Improved antimicrobial properties and enhanced plant protection	Scalability and economic feasibility	[146]

(continued)

Table 6 (continued)

Category	Prospects	Advancements and benefits	Challenges and considerations	References
Circular economy and waste utilization	Production of biopolymers from agricultural waste and microbial sources	Cost-effective, sustainable, and reduces reliance on petrochemical plastics	Process optimization, public acceptance, and industrial scalability	[147]
Advanced biopolymer blends and composites	Development of multifunctional composites for industrial applications	Improved mechanical and thermal properties, broader application potential	Processing efficiency and recyclability concerns	[148]
Hybrid and composite materials	Incorporation of agricultural fillers into polymer matrices	Improved strength, lightweight, and cost-effectiveness	Material compatibility, optimization of blending techniques	[149]
Biomedical applications	Use of plant-based biopolymers in drug delivery and tissue engineering	Biocompatibility, renewable material sources, and eco-friendly solutions	Long-term stability, regulatory approval	[150]
Microalgal biomass recovery	Application of bio-flocculants derived from plant-based biopolymers	Eco-friendly water treatment enhanced micro-algal harvesting efficiency	Optimization of flocculant properties and environmental safety	[151]
Performance enhancement in food packaging	Improving polysaccharide and protein-based biopolymer properties	Biodegradability, food safety enhancement, and reduced plastic waste	Mechanical property limitations, need for barrier function improvements	[152]

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Chapter 4

Biopolymer-Based Nano Formulations for Oral Delivery

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Abstract Biopolymers are among the most widely used nanomaterials for oral drug delivery applications. They are biodegradable, biocompatible, nontoxic and safer to administer through oral route. Oral route is most commonly used administration route for various types of medications as it eases to administer and easy to formulate compared to other route of administration. Integration of material science, nanotechnology and pharmaceutical science has led to the development of biopolymer-based nano formulations to overcome the possible limitations associated with orally administered drugs. In this chapter, we explored various biopolymers which are extensively used for formulation of oral nanocarriers including polysaccharide-based, protein-based, poly phenol-based and polyester-based polymers and their preparation methods. In addition, we have explored the various types of nanocarriers formulated with biopolymers for oral drug delivery applications, the challenges associated with them, various targeting strategies that could be used to overcome them and future trends in this field.

Keywords Biopolymer · Oral nano formulations · Polymeric nanoparticles · Chitosan nanoparticles · Nanosponges · Nanomicelles

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1 Introduction

Oral route of administration is widely accepted route of administration in majority of population. It is easy to administer, easy to formulate in case of oral formulations. It offers control of patient drug administration and dosage flexibility. Oral drug delivery systems have the highest market share with almost 50% of the global drug market [1]. This is the best route for drugs with shorter plasma half-life and have good absorption from the GIT. But there are certain limitations with the oral route of administration which are associated with the anatomical and physiological features of the gastrointestinal tract. The acidic environment of the stomach, gastric emptying, hepatic metabolism, requiring of high drug doses, drug interactions with the food highly influence the absorption, bioavailability and clinical efficiency of the drug [2].

Till now many strategies were developed to cope with the possible limitations with oral drug delivery. Nanotechnology-based drug delivery systems were in the forefront of the research for their incredible physicochemical properties which could revolutionize the drug delivery. Nano drug carriers offer several advantages such as enhanced water solubility in case of water insoluble drugs, prevent degradation, site specific delivery, prolonged in vivo circulation, controlled release [3]. But nanocarriers do suffer from limitations related to the toxicity, stability and storage. It is often reported that nanocarriers are capable of inducing oxidative stress [4]. Taking all these in to account, from the past few years there was a lot of research going on to identify potential nanomaterial which are capable of delivering drug effectively without inducing side effects or adverse events. In this regard biopolymers emerged as the materials which are capable of effectively deliver drugs as well as overcoming all the possible limitations with the oral route [5]. Because they are biocompatible, biodegradable, mucoadhesive and nontoxic, biopolymers—which come from biological sources make excellent oral delivery vehicles. In this chapter, we explored various biopolymers those are widely studied for oral drug delivery applications, nano formulations the preparation methods, targeting strategies challenges associated with biopolymers to better understand how far we have come and how far we have to go to make it to the global market.

2 Biopolymers

Biopolymers can be referred to the polymers which are either present naturally in the environment or artificially synthesized from the natural resources such as plants, animals, microorganisms [6]. These lengthy biomolecule structures are biodegradable and made up of monomeric units that recur in a chain-like pattern and are joined by covalent connections. Biopolymers generally have sugars, esters, amino acids and nucleotides as their monomeric units according to the type of polymer. There are various categories of biopolymers those exist in the nature which include proteins including bovine serum albumin, ovalbumin, gelatin and Zein; polysaccharides like

starch, cellulose, chitosan, pullulan, cyclodextrin, inulin and chondroitin; and organic polyesters like poly (lactic-co-glycolic acid), polycaprolactone and polylactic acid [6]. In addition, biopolymers can also be classified as synthetic and natural according to their origin or source [7]. Biopolymers have been widely used in various industries including ceramic and food for different applications. Because of biodegradable and biocompatible nature these compounds made their way into pharmaceuticals and has been revolutionizing the way we deliver medicines and the way we design the drug delivery systems. In this section, we will explore various biopolymers which have been extensively studied and used for preparing oral nano formulations.

2.1 Characteristics of Biopolymers for Oral Delivery

A good nanocarrier should be capable of delivering drug at the right place in right time in right quantity to produce desired results [8]. Biopolymers emerged as the materials which are capable of overcoming all the possible limitations with the oral route. The important characteristics a nanocarrier should possess when aimed to administer through oral route include biocompatibility, biodegradability, muco adhesion, acid stability and aqueous stability [9]. Muco adhesion means the ability to adhere to the mucosal surface which is provided by interaction between mucus layer and polymers. In order to maximize the therapeutic impact, this causes the drug carrier to adhere to the mucus layer and prolongs the dosage form's residence duration in the stomach mucosa. This permits a sustained drug release at a specific target site [10]. This also helps in localized delivery of the drug and improving drug absorption. Any drug intended to deliver through oral route should be stable in acid medium in order to avoid burst release of the drug. The biodegradability is required to release the drug from the nanocarrier while being biocompatible allows to avoid any toxic effects.

2.2 Classification of Biopolymers

Biopolymers intended for oral drug delivery were classified as natural and synthetic according to their origin. These are often classified as polysaccharide, proteins, polyesters and polyphenols based on their chemical composition. Majority of natural biopolymers include polysaccharides, proteins and polyphenols while synthetic or semisynthetic biopolymers include polyesters. These biopolymers can be prepared into various types of nanocarriers such as nanoparticles, nano vesicles, nanospheres, nanomicelles and nano capsules employing different types of preparation strategies. These biopolymers-based nano formulations exhibited significant advantages in invitro and in vivo. The biopolymers which are widely used for preparing oral nano formulations were given in Fig. 1.

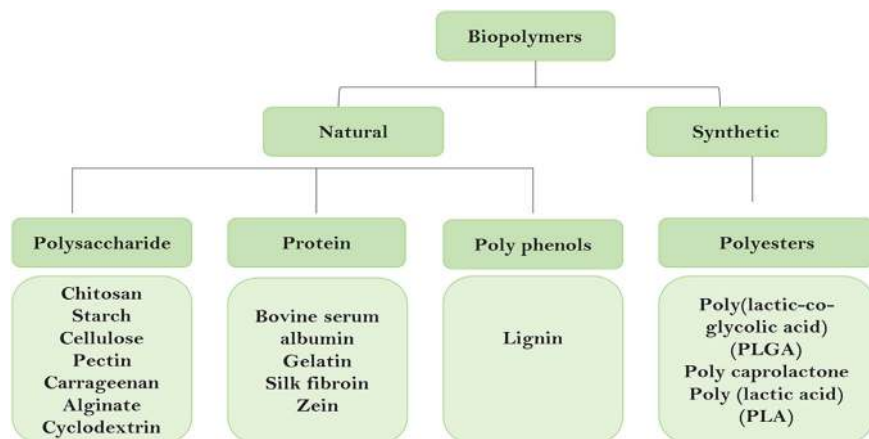


Fig. 1 Classification of biopolymers

2.3 Polysaccharide-Based Polymers

2.3.1 Chitosan

Chitosan, a cationic linear polymer derived from chitin, is found in insects, crustaceans, fungus and chlorophycean algae through the deacetylation process [11]. It has antifungal and antibacterial properties along with gelling property [12]. Chitosan's positive charge enables it to bind with negatively charged proteins, cell membranes and enzymes. This cationic nature provided by the amine groups aids in interacting with the mucus layer leading to the muco adhesion improving drug retention and absorption. These amino groups also make it easy to modify chitosan chemically to synthesize wide range of chitosan derivatives with different physicochemical properties. Because of its pH-responsive qualities, especially its pH-dependent swelling behaviour and solubility, chitosan can regulate drug release at different pH values, which is very helpful for oral delivery [13].

2.3.2 Starch

Starch is most abundant biodegradable polymer obtained from the plants and has been used in tissue engineering, medical devices, bone settings and drug delivery systems. Amylose and amylopectin are two distinct polymers that make up starch. Amylose is a straight or slightly branched polymer of glucose units bound by α -1–4 glycosidic bonds, whereas amylopectin is a branched biopolymer with additional α -1–6 glycosidic links. In general, a range of plant sources, such as corn, maize, wheat, potatoes, and green bananas, provide starch. Each of these has unique chemical composition, molecular structure, molecular weight, α -glucan chain length, amylose and

amylopectin content, amylopectin branching degree and non-carbohydrate impurity levels, in addition to other thermal and rheological characteristics [14].

For example, starch obtained from green bananas have higher amylose content making it resistant to acids and enzymes in the stomach and intestine than other sources. Because of this, it's a great option for oral delivery [15]. In the same way, maize starch has a higher capacity to form inclusion complexes with hydrocarbons compared to potato starch. This is beneficial for encapsulating and delivering lipophilic drugs, as the inclusion complex can protect the drug from degradation and facilitate controlled release [16].

2.3.3 Cellulose

The most prevalent biopolymer found in nature, cellulose comes from a different sources, including bacteria, fungi, algae and marine invertebrates. Glucose units linked by β -(1-4)-glycosidic bonds form this linear polymer [17]. Presence of hydroxyl groups makes it easy to chemically modify cellulose. Cellulose derivatives, including carboxy methoxy cellulose, microcrystalline cellulose and nanocrystalline cellulose, are currently being extensively researched for drug delivery applications. Nanocrystalline cellulose does not activate the immune system and is a biocompatible and biodegradable compound. Because of presence of hydroxyl groups, it can bind to multiple functional groups either covalently or non-covalently. Interestingly, NCC has rod like structure with size of 50–200 nm due to which it can avoid the filtration in kidney, further increasing its stability in the body [18]. Additionally, it can be removed in to cells from systemic circulation by macrophages strengthening its performance as a drug carrier. Other cellulose derivative is carboxy methyl cellulose an anionic water-soluble biopolymer with properties such as hydrophilicity, bio adhesive, pH-sensitivity, nontoxicity, gelling because of which it can release the drug in a controlled manner [19].

2.3.4 Silk Fibroin

Silk fibroin is a natural protein obtained from silk worms and a structural component of silk fibres known for its biocompatibility, strength, and biodegradability. It has a lot of beta-sheets, which give the silk fibres their stiffness, and polypeptide chains with molecular weights between 200 and 350 kDa. The glycoprotein, which gives the complete protein structure integrity, and the polypeptide chains made up of hydrophilic light chains and hydrophobic heavy chains with terminal C and N groups connected by disulphide linkages [20]. Silk fibroin is biocompatible, biodegradable and capable of encapsulating various types of therapeutic molecules. Presence of different types of functional groups enables chemical modification which helps in ligand mediated targeted drug delivery [21]. FDA has authorized it as a polymer that used as a DDS [22]. Silk fibroin nanoparticles maintain stability over a wide range of pH 5–14. It can remain stable even at pH below 5 at 0.2% concentration. These

nanoparticles have the ability to adhere to intestinal epithelial cells and gastrointestinal mucosa, endocytose and readily release the encapsulated substances into the bloodstream [23].

2.3.5 Pectin

Pectin is an anionic polysaccharide obtained from protopectin present in the plants and consists of 1,4-linked D-galacturonic acid units. Pectin is stable in acidic environment at pH 4 but it can be depolymerized by pectinase under alkaline conditions in the intestine. It undergoes deesterification at pH below 4 and results in reduced stability. It is highly resistant to proteases, and amylases in the upper gastrointestinal tract making it an ideal drug carrier for oral delivery. Pectin exhibits gelling activity by forming crosslinks with Ca^{+2} ions. Pectin molecules' carboxyl groups become protonated in the stomach's low pH environment, which causes the pectin layer to contract and compress, providing superior drug protection for oral administration methods [24]. Pectin is a safe, nontoxic drug carrier with good biocompatibility and bioadhesion. The structure and properties of pectin were hardly impacted by the gastrointestinal tract [25].

2.3.6 Alginate

Alginate is obtained from brown algae species such as *Laminaria hyperborea*, *Macrocystis pyrifera* and *Ascophyllum nodosum*. Depending on the type of algae, alginate has molecular weights between 32 to 400 kg/mol and varying G/M ratios and chain configurations [26]. Alginate can create stable, viscous solutions in water and is nontoxic, biocompatible and biodegradable. It interacts with Ca^{+2} ions and undergoes sol-gel transition under mild condition [27]. Even though alginate is advantageous it does suffer from shortcomings such as poor aqueous stability, uncontrollable degradation, weak mechanical properties. However, because alginates contain free functional groups like carboxyl and hydroxyl, they are easily chemically changed to get around these drawbacks. These alginate derivatives exhibit improvement in mechanical strength biodegradability and gelation property making it a versatile material for drug delivery applications [28].

2.3.7 Cyclodextrin

Cyclodextrins are cyclic oligosaccharides made up of α -D-glucopyranose units that are (α -1,4)-linked and obtained from starch by enzymatic degradation with glucosyl-transferase. Cyclodextrin has unique structure which can be described as a conelike structure with hydrophobic internal cavity and external hydrophilic surface. This structure enables formation of water-soluble complexes with poorly water-soluble drugs in the internal cavities of the cyclodextrins protecting the drug from enzymatic

and hydrolytic effects [29] stability. This often reduces the toxicity of drug, controls drug release and improves drug performance [30]. There are three types of cyclodextrins with varying number of units in its cyclic structure which are alpha, beta and gamma types, beta being the majorly used in drug delivery applications [31]. These are approved by USFDA and many countries and included in GRAS list as a food additive and natural product. Natural cyclodextrin has its own disadvantages such as poor absorption from gastrointestinal tract due to its hydrophilic nature. But this can be overcome by amphiphilic, cationic or anionic cyclodextrins which are chemically and structurally modified cyclodextrins. These enables formation of nanoparticles which could potentially influence the drug release, drug stability and solubility. Typically, techniques like polymer precipitation, solvent injection and evaporation, solvent diffusion and inotropic gelation are used to create cyclodextrin nanoparticles [32]. These nanoparticles are an excellent option for oral administration of medications that are poorly soluble in water.

2.4 Protein-Based Polymers

2.4.1 Bovine Serum Albumin

Bovine serum albumin (BSA) is a water-soluble protein obtained from serum of *Bos Taurus*. It has a molecular weight of 66,463 Da and is made up of 583 amino acid residues. At normal temperature, its isoelectric point in water is 4.7 [33]. It is highly accepted in the pharmaceutical industry due to its free availability, low cost, ease of purification and its similarity to human serum albumin. In BSA is non immunogenic, nontoxic and biodegradable making it an ideal nanocarrier systems for oral drug delivery. In addition, BSA nanoparticles exhibit high stability during in vivo conditions and storage. Furthermore, presence of high content of charged amino acids makes it easy to modify chemically by covalent binding or electrostatic adsorption. This feature makes it easy for BSA nanoparticles to bind to the ligands for surface functionalization which is essential for targeted drug delivery [34].

2.4.2 Gelatin

Gelatin is collagen in its hydrolysed form and approved by USFDA for food, cosmetics and pharmaceuticals. Lysine and arginine make up 13% of its positive charge, glutamic acid and aspartic acid make up 12%, while leucine, isoleucine, methionine and valine make up roughly 11% of its hydrophobic chain. Glycine, proline and hydroxyproline make up the remainder of the structure [35]. Biocompatibility, low immunogenicity, nontoxic degradation products, non-antigenicity, biodegradability, low cost, chemical modification potential, exceptional physiological tolerance, notable loading capacity, controlled drug release and good storage stability are the reasons gelatin became popular. The major limitation with gelatin is

its rapid dissolution in aqueous media which can be overcome by using chemical crosslinkers like carbodiimide, formaldehyde, glutaraldehyde. These crosslinkers make use of amino groups and form a strong amide bond which helps in increasing its mechanical strength, stability, reduce its aqueous dissolution while increasing its thermal resistance [1]. Additionally, gelatin is known for its mucoadhesive properties which makes it an important polymer for oral drug delivery.

2.4.3 Zein

Zein is an alcohol soluble protein obtained from maize consisting of a heterogeneous mixture of different peptides with four main fractions such as α -, β -, γ - and δ -Zein. 80% of the structure is composed of α -Zein while the remaining is made of other fractions. Zein is amphiphilic, water insoluble protein which dissolves in water only in the presence of elevated alcohol levels, urea or anionic detergents or at extreme pH conditions. This is attributed to the presence of glutamic acids and nonpolar amino acids such as proline, leucine and alanine. Zein is resistant to high temperature and has good oxygen barrier properties making it a suitable polymer for encapsulating of oxidation and temperature sensitive compounds [36, 37]. Previously many researchers demonstrated the potential of Zein nanoparticles in increasing the oral bioavailability of both small and large molecules. Additionally, hydrophilic polymers like polyethylene glycol can easily change the surface properties of Zein nanoparticles to prevent the formation of adhesive interactions with the mucus layer, increasing the likelihood that the particles will reach the intestinal epithelium [38].

2.4.4 Lignin

Lignin is a polyphenolic, amorphous, amphiphilic polymer obtained from plants and synthesized from phenolic derivatives [39]. Lignin is highly branched in nature and composed of three basic phenylpropane monomers such as syringyl, guaiacyl and *p*-hydrophenyl which are bound together with carbon-carbon bonds and ether bonds [40]. Lignin is biodegradable, biocompatible and nontoxic and also used as a stabilizer for emulsions due to its surface-active properties. It also possesses qualities including nonhemolytic action, low proinflammatory effects, antioxidant activity, antibacterial capability and low cytotoxicity. Lignin is less immunogenic because it avoids immunological and negative reactions [41]. Because lignin nanoparticles have a hydrophilic exterior and a hydrophobic core, they can be used to encapsulate hydrophobic medications. This enhances the solubility and stability of drugs and reduces the irritation to the stomach. Kraft Lignin, Lignosulfonate, Soda Lignin, Enzymatic Hydrolysis Lignin, Organosolv Lignin and Lignosulphate are among the different kinds of lignans that are utilized in drug delivery applications [42].

2.5 *Synthetic Polymers*

2.5.1 PLGA

One of the most popular biodegradable polymers for drug delivery applications is poly (lactic-co-glycolic acid) (PLGA). When PLGA is hydrolysed, it typically produces endogenous lactic and glycolic acids that the body metabolizes through the Krebs cycle with little toxicity. The European Medicine Agency (EMA) and the US FDA have approved PLGA for use in drug delivery applications. Commercial PLGA presents in different molecular weights and copolymer compositions, including PLGA 50:50, which is made up of 50% lactic acid and 50% glycolic acid [43]. To great extent, the properties of PLGA were influenced by the composition of glycolic acid and lactic acid. Furthermore, PLGA's free carboxyl end groups can be chemically modified to alter its rate of disintegration or drug delivery characteristics [44]. PLGA can be developed into nanoparticles easily due to its physicochemical properties and can cross the system barriers smoothly [45].

2.5.2 Poly Caprolactone

Polycaprolactone (PCL) is a semi synthetic and USFDA approved biopolymer for drug delivery applications. It is highly hydrophobic, biodegradable and highly biocompatible, nontoxic and non-mutagenic making it ideal for drug delivery applications [46]. It has slow degradation rate making it suitable for chronic therapy and prolonged drug release [47]. If required slow degradation rate can be enhanced by grafting PCL with water soluble polymers. PCL helps prevent particulate absorption by splenic or hepatic phagocytic cells and can readily encapsulate hydrophobic medications within the polymer bulk [48]. PCL can interact with other polymers easily which is make it easy for altering its physical and mechanical properties according to the requirements making it a versatile biomaterial for oral drug delivery.

2.5.3 PLA

The FDA-approved polyester poly (lactic acid) (PLA) has been widely employed as a polymeric matrix in drug-carrying nanoparticles. PLA nanoparticles are biodegradable and biocompatible and offer controlled drug release. Because the negative charges of the deprotonated carboxylic acid groups are electrostatically repelled, these are stable in aqueous media. But PLA NPs have certain limitations pertaining to their low chemical stability and hydrophobic nature which became significant when used for oral administration. This is because they are likely to be quickly removed by mucociliary clearance after being trapped by mucus because of steric or adhesive forces. Additionally, PLA NPs can precipitate in stomach fluid and are unstable in acidic fluids because to the protonation of the carboxylic acid groups at low pH,

which reduces electrostatic repulsion between particles and encourages precipitation. These limitations can be overcome during synthesis by surface coating polymers like PEG that could potentially increase their stability. Other than these limitations PLA allows easy chemical modification and enables targeted drug delivery [49] (Table 1).

3 Nanotechnology in Oral Drug Delivery

When scientist discovered that we can modify the physicochemical behaviour of the material by changing its structure at the nanoscale the way we utilized those materials have changed completely. Nanotechnology has gained a lot of popularity in various fields. Similar way in pharmaceutical science understanding the principles of nanotechnology led to the research into nanocarriers which changed the landscape of drug delivery. When compared to traditional drug delivery methods, nanocarriers have been shown to offer a number of benefits, including targeted anticancer drug administration, improved and accurate biodistribution and extended plasma half-life. Since nanocarriers are designed to recognize dangerous cells and deliver targeted drug release to them without interfering with healthy, normal cells, they anticipate consistent, direct, and controlled drug release to malevolent cells. [64, 65]. It describes how various nanomaterials are used to create a variety of nanocarriers for oral drug administration, including nanoparticles, micelles, liposomes, nanocrystals, carbon nanotubes, nanoemulsions, dendrimers and nanospheres. Both synthetic and natural polymers have been used in the creation of nanocarriers. Nanocarriers are colloidal drug delivery systems that use particles that are smaller than 500 nm, or submicron. Nanocarriers have been the focus of a lot of research in recent decades because of their great potential in the field of drug delivery. Because of their high volume to surface area ratio, nanocarriers are capable of changing the fundamental characteristics and bioactivity of drugs. Drug delivery systems can benefit from nanocarriers because of increased pharmacokinetics and biodistribution, enhanced solubility and stability, reduced toxicities, controlled release and site-specific drug delivery. The composition (inorganics, organic, or hybrid), size (large or small), shape (cube, sphere or rod) and surface characteristics (functional groups, surface charge, PEGylation, attachment of targeting moieties or other coating) of the nanocarriers can also be changed to change their physicochemical characteristics. Reducing side effects while effectively treating a problem is the ultimate goal of employing nanocarriers for drug delivery [66].

3.1 *Types of Nanocarriers*

1. Nanoparticles
2. Nanomicelles
3. Nanoemulsions

Table 1 Biopolymers used in preparation of oral nano formulations and their preparation methods source and physical chemical nature [50]

Polymer	Source	Nano formulation preparation methods	(Hydrophobic or hydrophilic)	References
Chitosan	Deacetylation of Chitin present in crustaceans	Ionic gelation emulsification and crosslinking, supercritical-CO ₂ -assisted solubilization, top-down approach spray drying self-assembly	Cationic (hydrophilic)	[51]
Starch	Maize Green banana	Gamma irradiation, high-pressure homogenization and ultrasonication, nanoprecipitation, acid hydrolysis, enzymatic hydrolysis	Hydrophilic	[52]
Cellulose	Plants, bacteria and tunicin	High-pressure homogenization method, acid hydrolysis, enzymatic hydrolysis, TEMPO oxidation method	Hydrophilic	[53]
Pectin	Protopectin	Ionotropic gelation, nanoemulsion, chemical reduction	Hydrophilic	[54]
Alginate	Brown algae macrocystis pyrifera, laminaria hyperborea and ascophyllum nodosum	Ionic gelation, emulsification, complexation	Hydrophilic	[55]
Cyclodextrin	Starch by enzymatic degradation with glucosyltransferase	Solvent injection, solvent evaporation, solvent diffusion, and inotropic gelation	Hydrophilic outer surface hydrophobic interior cavity	[56]
Bovine serum albumin	Bos Taurus	Desolvation, emulsification thermal gelation, self-assembly nano spray drying, nab technology coacervation	Amphiphilic	[57]
Gelatin	Collagen present in skin, bones and connective tissues of pig and cattle	Crosslinking, desolvation	Amphiphilic	[58]

(continued)

Table 1 (continued)

Polymer	Source	Nano formulation preparation methods	(Hydrophobic or hydrophilic)	References
Zein	Maize	Crosslinking, desolvation, flash nanoprecipitation, microfluidic process, dispersing	Hydrophobic	[59]
Silk fibroin	Silk worms	Desolvation, self-assembly, emulsion solvent evaporation	Hydrophobic	[60]
Lignin	Plants and biosynthesized from phenolic derivative	Self-assembly, dialysis, acid precipitation, high shear homogenization, ultrasonic method, enzymatic hydrolysis, interfacial polymerization/crosslinking, spray freezing method	Hydrophobic	[61]
PLGA	Either by direct condensation of LA and GA or by ring-opening polymerization of lactide and glycolide	Emulsification–diffusion, salting-out and nanoprecipitation	Hydrophobic	[62]
Poly caprolactone	Polymerization of the cyclic ester ϵ -caprolactone, which is frequently obtained from fossil fuels	Solvent displacement, nanoprecipitation, nanoemulsion templating method	Hydrophobic	[63]
PLA Poly (Lactic acid)	Cornstarch, sugarcane, sugar beet	Single, double and multiple emulsification Nanoprecipitation and solvent evaporation	Hydrophobic	[64]

4. Nanocomposite films

5. Nanosponges

3.1.1 Nanoparticles

Any material that is a particle size at least one dimension between 1 and 100 nm is called a nanoparticle (NP). They can consist of one or many atom (or molecule) species and have a range of size-dependent properties. Nanoparticles can lessen the energy state gap between bulk materials and microscopic molecules because of their wide size range [67]. A lot of treatments can only be administered parenterally. For chronic conditions that necessitate regular administration, oral administration

is a preferred option due to its convenience and higher patient compliance. One method being investigated to enable clinically viable oral administration is polymeric nanoparticles (NPs) [68].

The structure of nanoparticles is complex and consists of three outer lines: the shield sheet, which is composed of surface layers that can be coated with different trace metals, polymers, surfactants and other minute substances; and the inner part, which contains an inner component of the nanoparticle and typically corresponds to the nanosphere itself [69].

Sub-nanosized colloidal formations made of synthetic or semisynthetic polymers are called nanoparticles. Solid core spherical particles with a nanometric dimension are called nanospheres. They have a medication that is either adsorbed onto the surface or embedded in the matrix. A medication is effectively enclosed within the centre volume of nanocapsules, which are vesicular systems encased in an embryonic polymeric sheath. The majority of the drug is present in the nanocrystal solution system [70].

3.1.2 Nanoemulsions

Emulsions with droplets as small as 100 nm are called nanoemulsions. An emulsifier, water and oil are the usual ingredients of a nanoemulsion. Because it reduces the interfacial tension—that is, the surface energy per unit area—between the emulsion's water and oil phases, an emulsifier is required to produce tiny droplets. By means of steric hindrance and repulsive electrostatic interactions, the emulsifier also stabilizes nanoemulsions. Although proteins and lipids have proven useful in the creation of nanoemulsions, surfactants are typically employed as the emulsifiers. Many years of research have been focused towards the preparation of nanoemulsions employing an abundance of approaches, which are generally classified into two primary groups: high-energy and low-energy procedures. High energy methods, for instance ultrasonication and high-pressure homogenization, consume a lot of energy (approximate $108\text{--}1010\text{ W kg}^{-1}$) to generate tiny droplets. Conversely, low energy techniques use particular system characteristics to create tiny droplets with little energy consumption ($\sim 103\text{ W kg}^{-1}$). The emulsion inversion point (EIP) and the phase inversion temperature (PIT) are low energy techniques for producing nanoemulsions. In order to create nanoemulsions, some new technologies have recently been developed, including evaporative ripening and bubble bursting at the oil/water interface [71].

Nanoemulsion droplets exhibit narrow size distributions and are often between 20 and 200 nm in size. The creation of nanoparticles using a polymerizable monomer as the dispersal phase (also known as the heterogenous polymerization method), wherein nanoemulsion droplets serve as nanoreactors, is the primary use for nanoemulsions. New complex polymeric materials and hybrid organic/inorganic materials, such as magnetic polymeric nanospheres, are among the recently developed applications. [72].

3.1.3 Nanomicelles

Micelles are created when amphiphiles are submerged in water, and in the late 1960s, their readily controllable qualities and favourable pharmacological traits garnered a lot of interest. Micelles are composed of a hydrophobic core and an exterior hydrophilic surface that serves as a stabilizing interface with the surrounding aqueous environment. By merely adding new ingredients to the mixture of amphiphilic substances prior to micelle synthesis and by altering the preparation procedure, the size, charge and surface features of these carriers can be selected dependent on the delivery objective. Using micelles as drug carriers has several benefits, including the capacity to entrap sparingly soluble drugs, transport them to the site of action at concentrations that can surpass their intrinsic water solubility, and improve the drug's stability [73].

Polymeric micelles are enclosed by a single hydrophilic shell that contains numerous compartments on their hydrophobic cores. Micelles can be typical, snowman-shaped, two-hemisphere-shaped, cylindrical, reverse-shaped, like a dumb-bell and more, depending on their micellar structure. Different shapes, including worm-like, disc-like, sheet-like, or raspberry-like, etc. are also displayed by multicompartment systems [74].

3.1.4 Nanocomposite Films

Metallic nanoparticles are incorporated with various other substances, that involve polymers or ceramics, resulting in hybrid substances referred to as nanocomposites, that possess unique or upgraded characteristics. By combining the advantageous properties of their individual constituents, these materials produce innovative combinations of mechanical, electrical, optical and thermal properties [75]. The potential of metal nanocomposites to demonstrate distinctive characteristic combinations and innovative opportunities for design is one of their main attributes. For instance, metal-polymer nanocomposites are intriguing possibilities for conductive fillers and coating applications because they combine the considerable adaptability and manufacturability of polymers with the more favourable plasmonic, electrical and thermal properties of metals [76]. Nanocomposites are composed of by combining multiple stages of dimensions at the nanoscale embedded within a matrix containing metal, ceramic or polymer. Metallic, ceramic and polymer matrix. Nanocomposites are the three main categories of nanocomposites. Biomedical applications have made substantial use of polymer nanocomposites. Because they may form supramolecular and self-assembled morphologies, organic polymers and inorganic nanoparticles make good building blocks for creating nanocomposite hydrogels. A nanocomposite's properties are influenced by its loading, matrix, degree of dispersion, shape, size and orientation of the nanoscale phase, as well as the interaction between the matrix and the nanoscale phase [77].

3.1.5 Nanosponges

Nanosponges are mesh-like structures, microscopic, that may hold a different substance, including pharmaceutical compounds. They enhance the solubility of drugs that are soluble in water and lipids and have a spherical colloidal shape [78]. With a backbone of long-chain polyesters in the solution and crosslinkers joining different polymer components, they resemble a three-dimensional network [79]. With extended drug release, they improve the bioavailability of medications. The amphiphile character of nanosponges allows them to carry both hydrophobic and hydrophilic molecules due to their external hydrophilic branching and internal hydrophobic chambers [80]. Easy reproducibility across a range of treatments, such as stripping with reasonably safe hot gases, cleaning with environmentally friendly solvents, light heating and altering ionic strength or pH, are some advantages of nanosponges [81].

3.2 *Advantages of Nano Formulations in Oral Drug Delivery*

Increased drug solubility: By offering a wide surface area for drug dispersion, nano formulations improve the solubility of medications that are not very soluble in water. This increases the drug's rate of solubility and, in turn, its absorption.

Increased bioavailability: Nano formulations small size enables effective absorption through biological barriers, which raises bioavailability. This is especially advantageous for medications with poor systemic absorption.

Degradation protection: Nano formulations can protect medications from harsh gastrointestinal conditions and enzymatic degradation. A greater proportion of the given dose will enter the bloodstream undamaged because to this protection.

Regulated release: By enabling sustained and regulated medication release, nano formulations maximize therapeutic efficacy and minimize the need for frequent dosing. For medications with limited therapeutic windows, this is essential.

Surface modification for targeting: Site-specific medication delivery is made easier by adding ligands or targeting moieties to the surface of nano formulations. By guiding the medication to its precise location of action, this method improves the therapeutic index [82].

3.3 Barriers to Oral Absorption and How Nanocarriers Help Overcome Them

The main challenge for oral medication administration by nanocarriers is that the integrated drug must first pass through a number of the body's natural barriers before the nanocarrier can get to the target cell. The nanomaterial will protect the medication from the acidic environment and proteolytic "thunderstorm" of the stomach after it has been taken. The nanocarrier leaves the stomach and enters the small intestine, passing via the duodenum, jejunum and ileum. Either the cargo must be released for intestinal absorption in this scenario, or the nanocarrier itself must be absorbed. Otherwise, the nanocarrier will inevitably be eliminated from the human body due to the colon's inability to absorb solid molecules. While the small intestine is adsorbing the nutrients, the colon simply reduces the water content of the faeces. The nanocarrier must pass through the layer of epithelial cells after this uptake in the small intestine in order to reach the lamina propria. The next barrier is a layer of the blood vessel's endothelial cells, which the nanocarrier must pass through to get to the blood vessel lumen. Two outcomes are possible when the nanocarrier enters the bloodstream. The medication may be delivered to a target cell or discharged straight into the bloodstream. The second option, however, has two more obstacles: accessing the target cell and passing through endothelial cells to leave the bloodstream.

Crossing several cellular boundaries is essential for oral medication administration using nanocarriers. Through the use of desmosomes, adherens junctions and tight junctions, epithelial cells are able to form a barrier. When all of this is combined, there is almost no room between the cells. These characteristics are achieved in endothelial complexes by adherens, gap and tight junctions. While endothelial cells are found only on the inside surface of blood and lymphatic arteries, epithelial cells are found in almost every tissue. Both serve as a biological defence system for the underlying tissue. Despite their diverse morphologies, nearly all endothelial and epithelial cells are polarized and have an apical and a basal side. One of the most challenging aspects of employing nanocarriers for medication delivery is overcoming these barriers. As a result, developing nanomedicines requires a fundamental comprehension of the molecular pathways that enter and pass-through endothelium and epithelial cells [83].

4 Formulation Strategies

There are various formulation strategies for preparing biopolymer-based nanocarriers depending on the type of polymer (polysaccharide or protein or poly ester), type of nanocarrier (nano particles or nanosponges or nanomicelles). Here, we discussed preparation methods majorly used for synthesizing polymeric nanoparticles (Fig. 2). Other than below-mentioned formulation methods advanced techniques like microfluidic technology are now being widely explored for preparing

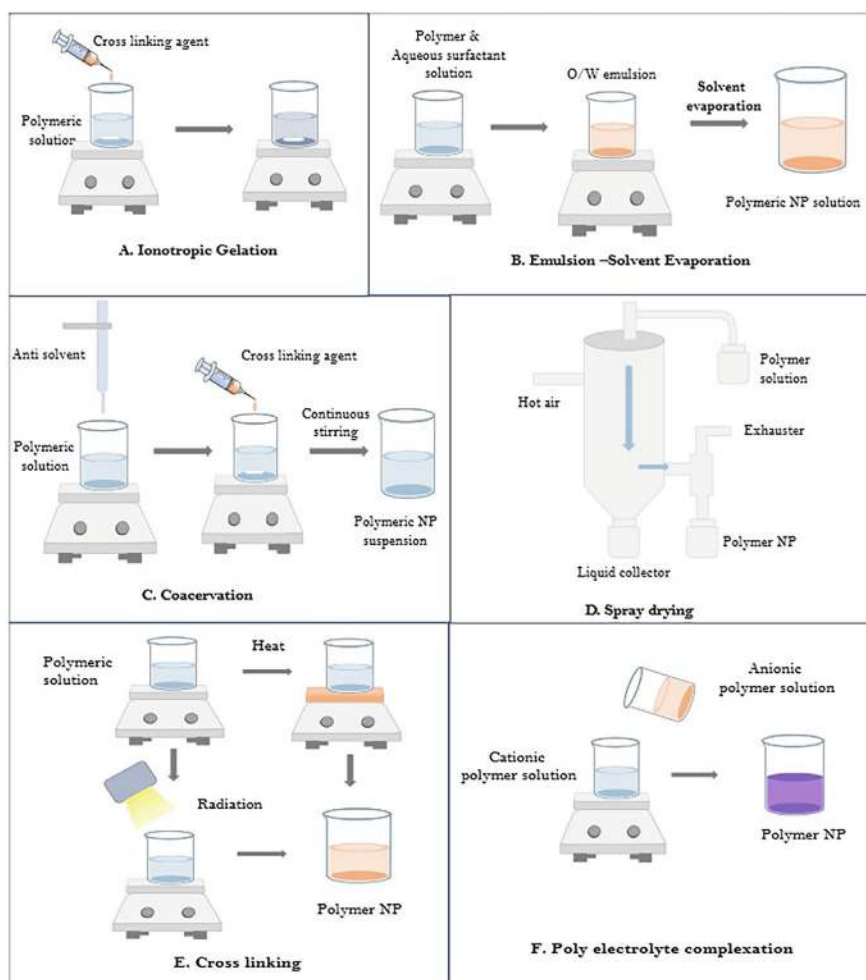


Fig. 2 Formulation strategies of polymeric nanoparticles

biopolymer-based nano formulations since it provides exact control over the size, content and form of nanoparticles.

4.1 Ionotropic Gelation

Based on the electrostatic interactions between ions with different charges, the ionic gelation technique was invented in 1997 as a chemical method to produce microparticles, or NPs. This process requires a polymer, usually chitosan and alginate. Under stirring conditions, TPP solution is added to CS and/or diblock copolymer of ethylene

oxide and propylene oxide, depending on the mass ratio of CS/TPP or the molecular weight of CS. This produces CS-NP particles, which have a zeta potential of 20 to 60 mV and a size range of 200 to 1000 nm. This hydrogel formation is identified due to the electrostatic interactions between the amino group of CS and the polyanion group of TPP. Furthermore, tetanus, diphtheria toxoid (vaccine) and bovine serum albumin (protein) were all successfully loaded into NPs in these investigations [84].

This general method of producing microparticles, or NPs, entails the mechanical stirring of at least one polymer while opposite charge types interact electrostatically [85]. The synthesis of NPs was based on the records of anions, such as ferrocyanide and ferricyanide salts, sulphate salts (Na, Mg, or octyl-, lauryl-, hexadecyl-, cetostearyl-) and polyphosphate salts (pyro-, tri-, tetra-, octa- and hexameta-), as well as polymers, including chitosan, carboxymethyl cellulose, collagen, dextran, fibrin, gellan gum, hyaluronic acid, sodium alginate and pectin. Among these, TPP (anion) and CS (polymer-cation) are the two most frequently used. Additionally, to boost their effectiveness, medications or bioactive compounds might be enclosed within an NP matrix [85–87].

4.2 Emulsion-Solvent Evaporation

An organic phase is created by dissolving the drug Ketoprofen with the polymer Eudragit E100 or RS in 10 millilitres of acetone. This organic phase is combined with an aqueous phase containing a surfactant (PVA, concentration 0.5%, 90 mL) to produce an O/W type emulsion. The volume ratio between the water and oil phases is 1:9. This emulsion is broken up into nanodroplets by applying external energy using a sonicator. These nanodroplets become nanoparticles upon evaporation of the highly volatile organic solvent. The organic solvent evaporates after two hours of magnetic stirring in an environment at 300 rpm. The effects of various processing parameters on particle size were examined. Processing parameters include the volume ratio of the water and oil phases, the concentration of PVA in the aqueous phase, and the concentration of polymers in the organic phase [88].

4.3 Coacervation and Phase Separation

By using liquid–liquid phase separation, the coacervation process creates polyelectrolyte from a homogeneous solution, which in turn causes coacervate to develop around the active ingredient. When crosslinking with enzymes like transglutaminase or adding the right chemical, the coacervate can rise [89]. Numerous factors could affect the complex formation and interaction between the polymers, including the type of biopolymer, concentration, pH, electrostatic contact and ionic strength [90]. Complex coacervation is created when different NCs and food supplements are

encapsulated using the coacervation process. Among the many benefits of the coacervation approach are its ease of scaling up and the fact that it requires no equipment or solvents [91].

4.4 Spray Drying and Freeze Drying

A well-known method for creating dried powdered goods is spray drying (SD), which involves quickly evaporating water from an atomized liquid that is supplied into a spray chamber. Water is evaporated from the atomized particles by hot air flowing either counter-currently or co-currently inside the chamber, turning the wet input into a dry powder. Spray drying is useful for producing free-flowing powders with a controlled range of particle sizes at a quick drying speed. Despite the benefits described above, the high input temperatures of the process might result in significant losses of volatile chemicals and thermal degradation of materials that are sensitive to heat [92].

However, one issue that freeze drying (FD) immediately addresses is the preservation of heat-labile components. In the FD process, the material is first frozen at a low temperature to create ice crystals. These crystals are sublimed from the solid state directly into the vapour phase in a vacuum chamber using a method known as primary drying. The temperature and vapour pressure must be maintained below the triple point of water in order for sublimation to occur. The next step in further lowering the sorbed water that remains in the solute matrix (the freeze concentrated non-ice phase) is desorption, often known as secondary drying. The sublimation of ice crystals creates porous structures, which improves the powdered product's rehydration properties. Although the product quality of the freeze-dried particles is normally high, the use of the freeze-drying technology is limited by its batch nature, lengthy drying times, high vacuum, low temperatures and consequently high operating costs [93].

4.5 Polyelectrolyte Complexation

Functional materials with polyelectrolyte incorporation have become innovative adsorbents for the efficient removal of contaminants from water and wastewater in recent years. A unique type of polymers containing lengthy chains of repeating charged molecules are called polyelectrolytes (PEs). Aqueous solutions of oppositely charged PEs are mixed to create polyelectrolyte complexes, or PECs [94].

When a polymer complex develops with other oppositely charged polymers, it produces polyelectrolyte complexes, which have unique physicochemical properties and great biocompatibility. The polyelectrolytes themselves are categorized as cationic, anionic, or non-ionic based on the kind of macromolecules they produce, the forces that interact between the complexes, and the kind of functional group that

is present at the polymer chain. Furthermore, these natural compounds reduce toxicity by avoiding the need for chemical agents to cross-link polymeric chains. Their sustainable and useful way of delivering highly water-soluble medications, which enables them to target therapeutically active moiety to the site of action, has led to a number of applications in the biomedical, pharmaceutical and nanobiotechnology industries [95].

4.6 Crosslinking and Grafting Methods

The cost-effective technique of polymer crosslinking has drawn increased interest. Both thermal and radiation crosslinking are covered in the section on polymer crosslinking. In addition to improving ionic conductivity and stabilizing the amorphous phase at ambient temperature, crosslinking can prevent the deterioration of mechanical properties brought on by the adoption of a low glass transition temperature chain as the skeleton structure. Through a sequence of processes, crosslinking transforms linear polymers with reactive activity into three-dimensional network polymers. A double polymer network (PVDF-HFP and PEO) was shown to be the framework for improving ion conductivity and mechanical strength through UV crosslinking. While the PVDF-HFP matrix promotes better mechanical qualities, the PEO matrix offers the tunnel for cation migration [96].

5 Targeting Strategies

5.1 Surface Modification for Enhanced Muco Adhesion

Muco adhesion is one of the important properties that a polymer should possess to effectively deliver drug through oral route. It enables drug absorption through the gastrointestinal mucosa. Most of the biopolymers have mucoadhesive properties. But certain polymers such as PLGA, PCL lack required mucoadhesive action. PLGA's nanoparticles are prevented from adhering to the intestinal mucosa by the electrostatic repulsion between the negatively charged polymer and the negatively charged intestinal surface (caused by sialic acid). Surface coating the polymeric nanoparticles with mucoadhesive polymers like chitosan is an important strategy to improve the muco adhesion. Numerous studies have previously documented an increase in PLGA nanoparticles' zeta potential following chitosan coating, which boosts the mucoadhesive capacity and cellular absorption [97]. This happens due to chitosan possess OH and NH₂ groups which forms hydrogen bonds with the mucin present in the intestinal mucus at pH 6–7.5. These interactions enable strong adhesion between chitosan and mucin. Additionally, chitosan is known to be capable of opening epithelial tight junctions and allows uptake of hydrophilic drugs (Fig. 4) [98].

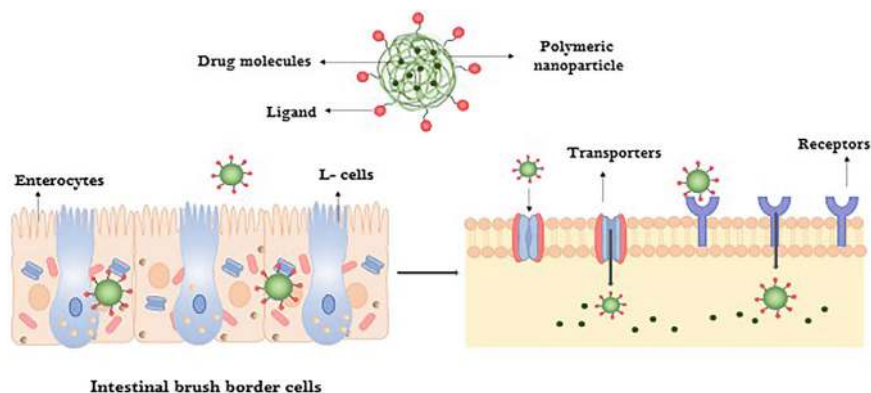


Fig. 3 Ligand mediated targeted drug delivery in intestine with biopolymer-based nano formulations

5.2 *Ligand-Conjugated Biopolymers for Site-Specific Delivery*

In ligand-mediated delivery, ligands that can target particular receptors, transporters or specialized intestinal cells are used to decorate the carrier's surface (Fig. 3). The mechanism of delivery of drugs into intestinal epithelium involves two pathways one is through enterocytes and other is through specialized cells such as M cells and goblet cells. Entry of enterocytes involves receptor mediated endocytosis which is the prime area of focus for research to deliver the drugs effectively through the intestinal cells and to the intestinal cells [99].

In general ligand mediated delivery can be used for intestinal specific delivery or to target other organs or tissues. For instance, brain can be targeted by the ligands specific to the receptors expressed on brain surface such as lactoferrin, GLUT transporters, apolipoprotein E, and lectin. For example, in one study the researcher developed apolipoprotein-E coated BSA nanoparticles loaded sumatriptan. Sumatriptan was effectively crossed the BBB due to surface modification with apolipoprotein and effectively reduced the symptoms of migraine. Similar to this, receptors found on the surface of intestinal cells can be used to target intestinal cells. The primary receptors that became point of research for many researchers include transferrin receptors, folate receptors, mannose receptors, CD98, CD44, macrophage galactose lectin, PepT1, F4/80 [100].

5.3 *pH Responsive Drug Delivery Systems*

The pH of the GIT falls varies from mildly alkaline in the intestine to acidic in the stomach. For a biomaterial to effectively delivery the drugs through oral route, it

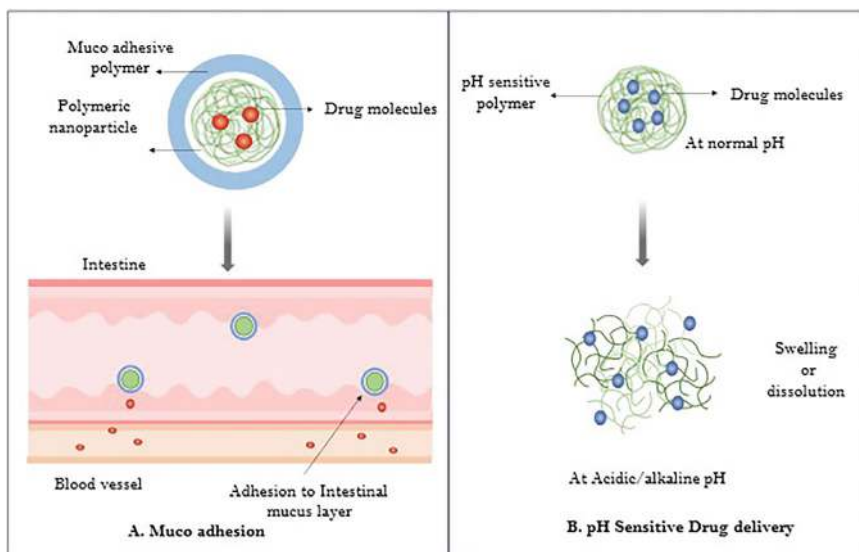


Fig. 4 Mechanism of muco adhesion and pH sensitive drug delivery

should be stable at the acidic pH and capable of release the payload in a controlled manner. Interestingly, certain polymers act differently in different pH which can be exploited for preparing pH sensitive nanocarriers. Generally, two types of mechanisms of drug release were observed with pH sensitive nanoparticles in different pH. Polymers such as poly (methacrylic acid), poly (acrylic acid) grafted poly (vinylidene fluoride) and hydroxypropyl methylcellulose phthalate cause drug release at higher pH levels because of ionizable functional groups on the side chain or backbone of the polymer. This type of nanoparticle is commonly used in the delivery of oral medications, where a physiological pH shift in the GI tract facilitates the swelling or dissolution of the carriers. The other type of pH-sensitive nanoparticles behaves in the opposite way from the former in terms of swelling or dissolving. Since it swells in acidic conditions, it can be utilized to target endosomes, lysosomes and tumours when the pH is rather low (Fig. 4) [101].

5.4 PEGylation

One common polymer for oral medication delivery systems is chitosan. While it is soluble in acidic settings, it is poorly soluble at neutral or alkaline pH levels. Another drawback of chitosan nanoparticles is that they are easily removed from the bloodstream by the reticuloendothelial system (RES) and are vulnerable to serum nucleases, which significantly lowers their in vivo circulation [102]. Another popular polymer for oral nano formulations is silk fibroin, which can aggregate

[103]. Among the difficulties encountered by certain biopolymer-based nanoparticles include low solubility, stability and opsonization as well as posterior phagocytosis by the mononuclear phagocyte system. PEGylation, or the surface coating of nanoparticles with PEG, has become a successful way to address these issues. PEG is a water-soluble, amphiphilic polymer that dissolves in distilled water and is primarily used to chemically alter both natural and artificial macromolecules for a variety of uses. PEG's chemical reactivity comes from the active hydroxyl groups at both ends of the chain, which can interact with functional groups such as carboxylic, amine, hydroxyl and ester groups [104]. Many studies have reported that PEGylated nanoparticles have exhibited increased stability, solubility, reduced clearance for the systemic circulation, enhanced in vivo circulation, cellular uptake and enhanced therapeutic efficacy.

6 Challenges and Future Perspectives

6.1 *Stability and Scalability Issues*

Among the obstacles still standing in the way of commercialization is biocompatibility. Ensuring that biopolymer based nanodrug delivery systems are biocompatible is crucial, as certain polymers may be toxic or elicit immunological responses. Additionally, preserving the nanoparticles' stability throughout storage and transit is essential to their efficacy in medication administration. Scalability is the problem. Increasing the production of biopolymer-based nano-drug delivery systems for commercial usage while maintaining their quality and consistency is one of the most difficult tasks [105].

Even with improved stability controls, scalability remains a significant barrier to the practical implementation of biopolymer-based nano-drug delivery systems with antioxidative properties. The process of increasing output from laboratory-scale to commercial-scale amounts while preserving quality, consistency and cost-effectiveness is difficult and calls for meticulous raw material, equipment and manufacturing process optimization. For example, the creation of reliable and repeatable manufacturing protocols is necessary when moving from batch production techniques, which are usually employed in research landscape to continuous manufacturing processes needed for large-scale manufacturing. Furthermore, variations in production circumstances, material qualities and equipment capabilities across laboratory and industrial settings can provide scalability issues. In order to overcome scaling issues, interdisciplinary cooperation among scientists, engineers and business experts is necessary to improve production procedures, resolve technical constraints and guarantee regulatory compliance. Furthermore, scalability can be improved and production processes streamlined with investments in quality assurance systems, process automation and modern manufacturing technology. Overall, when

implementing biopolymer-based nano-drug delivery systems in industry, preserving nanoparticle stability and attaining scalability are crucial factors [106].

The stability of nanoparticles during storage and transit is essential for their successful application in large-scale medication administration within the framework of industrial translation. In general, when exposed to different environmental circumstances such as temperature variations, light exposure, or mechanical stress during storage and transportation, nanoparticles are very prone to degradation, aggregation, or changes in physicochemical attributes. Any change in the stability of nanoparticles can reduce their ability to distribute drugs effectively, which could result in uneven therapeutic results. In order to monitor and preserve nanoparticle stability during the manufacturing process, certain quality control procedures must be put in place. Enhancing formulation elements including the choice of biopolymer, antioxidant substances, solvent and stabilizing agents is necessary to increase nanoparticle stability and prevent aggregation or disintegration. Additionally, to reduce exposure to the environment and maintain the integrity of nanoparticles throughout storage and transit, suitable storage conditions and packaging materials must be chosen [106].

6.2 *Regulatory and Intellectual Property Challenges*

There are still some obstacles preventing the widespread usage of biopolymers. Certain products poor mechanical properties, quick disintegration and high hydrophilic capacity make them difficult to use, particularly in humid or unfavourable conditions. Furthermore, by taking into account the inherent qualities and susceptibility of the chosen strain, this will optimize the entire process and reveal methods for creating the ideal formulation using preclinical, in vitro and in vitro methods that take into account capsule release, production, packaging, shipping and storage. First, more in vivo and clinical studies are required to show the health benefits of biopolymers and their biocompatibility in a range of biomedical applications, particularly when they are used as encapsulation materials for drug delivery, as the majority of research to date has been done in vitro.

6.3 *Translational Gaps from Lab to Clinic*

In this rapidly evolving field, financial concerns, economic considerations and the disparity between policy and worldwide adoption of the new technology must all be addressed. The use of biopolymers such as PLA, silk and chitosan is the subject of growing research interest in medical applications. The special qualities of biopolymer nanocomposites, such as their enhanced structural and functional characteristics, nontoxicity, biocompatibility and biodegradability, make them very fascinating. These new materials are highly significant in medicine, as synthetic materials do not fully meet the requirements of living systems [107].

7 Future Trends: Stimuli-Responsive, Smart Polymers, AI-Guided Formulations

The quality of healthcare is the primary goal for scientists, and technology is changing daily. Drug delivery and therapy have always been the main concerns of scientists because it has always been difficult to provide medications effectively and efficiently. Toxicology, lack of specificity, low bioavailability, short drug delivery, side effects, quick disintegration, and invasiveness are the main problems with medication delivery. New strategies must be developed to produce drug delivery systems (DDS) that are nontoxic, selective, and capable of delivering prolonged drug administration with improved bioavailability. Biopolymers in DDSs aid in resolving issues related to biodegradability and biocompatibility. However, new approaches are still needed to address these issues that the DDSs are facing. Scientists have turned their attention to nanotechnology as a solution to the problems with traditional DDSs. Consequently, it has been seen that the trend towards drug delivery (DD) has shifted in favour of nanotechnology-based drug delivery systems (NDDSs). The success of these systems can be attributed mostly to their nanoscale design. Additional important characteristics are nontoxicity, biocompatibility, free mobility because of the nanosize and flexibility in the system's component composition [50].

8 Conclusion

Biopolymers have become quite popular because they are nontoxic, biocompatible, biodegradable, and most importantly they can change how drugs are released. Even before nanotechnology-based drug delivery systems came into existence, biopolymers were widely being used in conventional oral delivery systems like tablets and capsules. Biopolymers such as cellulose and its derivatives like carboxy methyl cellulose, micro crystalline cellulose, hydroxy methyl cellulose used for modifying drug release rate, starch was used as binder in tablets. Protein based polymers like gelatin was used for preparing capsules. For long period, they have been used for oral drug delivery resulting in better understanding of they behave in a biological environment. But nano formulations are different from conventional formulations in terms of their physicochemical properties and biological behaviour. There is a lot of research going to study the in vivo behaviour of polymeric nano formulations in animal models but the clinical translation is poor. There are no major biopolymeric nanoparticle-based nano formulations in the market which could be due to the fact that the synthesis of nano formulations is expensive and there is growing concern about the potential toxicity issues with the nano formulations. There is a need for more research into this area to leverage the potential benefits these biopolymers-based nano formulations for effective and targeted oral drug delivery that could improve overall outcome of the therapy.

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Chapter 5

Cellulose-Based Drug Delivery System for Protein and Peptides

Bhumika Parashar, Rishabha Malviya, and Musarrat Husain Warsi

Abstract Proteins and peptides offer high therapeutic specificity but face challenges like enzymatic degradation and low bioavailability. Cellulose-based carriers provide stability. This chapter explores cellulose-based drug delivery systems, their mechanisms of drug loading and release, and their applications in oral, injectable, transdermal, and mucosal delivery. Cellulose derivatives protect proteins, enable controlled release via diffusion, pH sensitivity, and enzyme-triggered degradation, and support advanced delivery strategies like stimuli-responsive materials and 3D-printed scaffolds. Cellulose-based systems enhance protein and peptide drug delivery but require further research on scalability, regulatory approval, and stability for clinical applications.

Keywords Cellulose derivatives · Hydrogels · Protein stability · Peptide delivery · Enzymatic degradation · Controlled release · Nanoparticles · Stimuli-responsive delivery · 3D printing scaffolds · Chemical conjugation · Physical encapsulation · pH-sensitive release · Hydroxypropyl methylcellulose · Carboxymethyl cellulose · Injectable hydrogels · Oral delivery · Transdermal delivery · Mucoadhesive systems · Biocompatibility · Regulatory challenges

1 Introduction

Peptides and proteins are now slowly changing the shape of modern medicine due to the high specificity with which they can produce therapeutic effects as compared with small-molecule drugs and the ability to affect biological pathways that small molecules cannot reach Fig. 1 [1, 2]. A few examples of diseases that are benefiting

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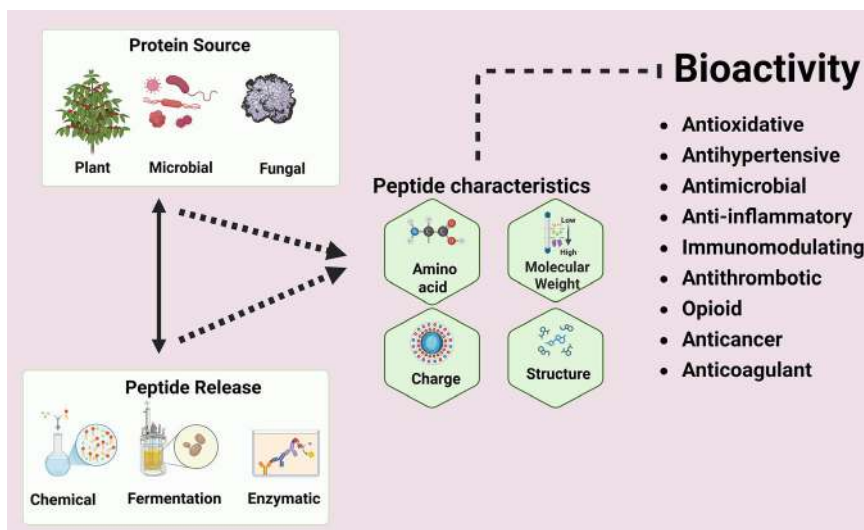


Fig. 1 Unveiling bioactive proteins and peptides: from source to function

greatly from peptide and protein therapy are diabetes, cancer, autoimmune diseases, and infectious diseases. Imagine the volumes of clinical utilization for this substance: insulin, monoclonal antibodies, and peptide-based vaccines. Importantly, such great therapeutic applicability has been coupled with high obstacles for the delivery of drugs like proteins [3]. The reason is that it is hydrophilic, very large, and susceptible to degradation by enzymes, which limit its bioavailability [4]. Quick degradation by proteolytic enzymes in the GI tract after oral administration leads to deficient absorption since they cannot cross the intestinal epithelial barrier. Most drugs are administered parenterally, through direct injection into a vein or under the skin [5]. However, this mode of administration results in rapid clearance and, thus, necessitates frequent doses that hamper patient compliance. Proteins are very sensitive to temperature and mechanical stress as well as pH changes; hence, it is of utmost importance to keep proteins stable during the processes of formulation, storage, and administration. To combat these problems, we require newer drug delivery systems that will stabilize and safeguard proteins and peptides and allow controlled or targeted release [6]. Cellulose-based materials have recently been subjected to extensive studies that investigate their potential drug delivery system for effectively delivering proteins and peptides due to their compatibility and some marvellous physicochemical characteristics [7]. Cellulose constitutes a naturally occurring polysaccharide, making a very stable and organized polymer from the units of D-glucose, which are linked by β -(1 $\rightarrow$ 4)-linkages. Hence, with the low solubility of parent cellulose, the chemical modification of cellulose derivatives provides tunable parameters that favour drug delivery [8]. Encapsulating proteins and peptides in polymeric cellulose systems prevents enzymatic breakdown and slows down the release at the location of the target. Cellulose derivatives offer so many designs for drug delivery systems, such as

nanoparticles, hydrogels, films, and scaffolds, thereby allowing for wide flexibility for different routes of administration [7]. Thus, their hydrophilic matrix formation would allow the delivery of drugs over an extended period, thus promoting adherence to treatment and reducing the frequency of dosage. Importantly, cellulose-based carriers can be manipulated to interact with environmental stimuli, including temperature, pH, or enzyme activity, so that drugs can be released in a controlled manner and at the site of interest [9]. Another outstanding benefit of cellulose-based drug delivery systems is their excellent biocompatibility. Cellulose qualifies for use in biomedicine given that it is a naturally available polymer, unlike synthetic polymers, which are known to cause harmful immunological reactions and toxicities [10]. Yet another commendable feature is that it is biodegradable. This tremendously eases concerns about the buildup and environmental effects caused by carriers being stored for too long, as cellulose-based carriers will slowly decompose into non-toxic by-products. Cellulose has excellent physical and chemical stability, which is another very important consideration for keeping peptide and protein drugs from degradation [11]. In contrast to other polymeric carriers that may degrade prematurely or have negative interactions with therapeutic agents, cellulose maintains a stable environment that preserves the bioactivity of encapsulated biomolecules. A further significant advantage is the ability to achieve controlled drug release from such carriers. By modulating the chemical and structural properties of cellulose, delivery systems can be designed to deliver proteins and peptides in a controlled manner [7]. This prevents drastic fluctuations in drug concentrations and maintains therapeutic efficacy over time. This kind of controlled release system was specifically important in the treatment of chronic diseases, where a steady level of drug is essential for success. In a nutshell, peptides and proteins exhibit excellent therapeutic properties, yet they are difficult to deliver due to their instability, rapid rates of enzymatic degradation, and clearance. Indeed, cellulose-based materials hold much promise regarding their use as platforms to deal with these problems by protecting and stabilizing, controlling the release, and biocompatibility delivery of proteins and peptides [12]. Due to this versatility, they would serve well in developing new systems for the delivery of protein and peptide drugs, which can improve treatment and outcomes for patients. Research into more cellulose-based drug delivery methods will hold promises of the new biopharmaceuticals that would result from further studies into the improved applications of proteins and peptides.

2 Cellulose and Its Derivatives in Drug Delivery Applications

The traditional form of cellulose and its derivatives, such as cellulose ethers, cellulose esters, and oxycellulose, are widely utilized in numerous drug delivery systems [13]. Cellulose ethers include a substantial category with five principal derivatives: MC,

carboxymethyl cellulose (CMC), hydroxypropyl cellulose (HPC), ethylcellulose (EC), and hydroxypropyl methyl cellulose (HPMC).

2.1 Cellulose Ethers

Cellulose can be chemically modified in a significant way through the etherification reaction. The pharmaceutical industry relies heavily on the produced cellulose ethers as essential excipients in the production of matrix tablets. The hydrogel layer encasing the medicinal core expands as the cellulose ethers start to hydrate upon delivery [14]. As a diffusional barrier, the hydrogel layer allows water molecules to enter the tablet matrix, facilitating medication release. Cellulose ethers can be synthesized under alkaline circumstances utilizing several reagents containing alkoxy groups. Chemical structure and substituent group distribution affect cellulose ether surface activity, viscosity, and solubility. With increasing substitution, ethers move from water (DS 1.0–2.3) to organic solvents (DS 2.3–3.0). Many others have varying solubility properties, which causes their encapsulated medications to be released in diverse ways [15].

2.1.1 Hydroxypropyl Cellulose (HPC)

The anhydrous glucose chain of propylene oxide reacts with alkali cellulose to produce HPC. In addition to cold water, HPC dissolves in several organic solvents [16]. This results in HPC being a useful component of the drug release system as a thickener or tablet-binding agent [17].

Drug delivery systems (DDS) depend on an external gel layer to control excipient drug release. If the excipient polymer gels gradually, the solvent may quickly dissolve the drug through the glassy matrix. Synthesized gels must be strong to produce a protective barrier that controls medication release. Excipient polymer content, viscosity, and chemical composition largely determine the characteristics. In high-performance computing (HPC), employing excipients just as a matrix layer is ill-advised. In combination with other polymers, they can change drug release. Utilizing water-insoluble EC, HPC was said to accurately regulate the release rate of the water-soluble medicament, oxprenolol hydrochloride solid dosage [18]. The drug release rate and its adsorption dose on the polymer may exhibit a linear association.

Yamada et al. utilized HPC-based co-grinding technology to improve the solubility rate of 3, 9-bis (N, N-dimethylcarbamoyloxy)-5H-benzofuro [3, 2-c] quinoline-6-one (KCA-098), a new benzofuroquinoline derivative noted for its insufficient oral absorption [19]. The particle size of KCA-098 can be significantly reduced through grinding with HPC, leading to an improved dissolving rate and extended supersaturation duration. The drug would be distributed optimally and released in liquid solutions. Desai et al. employed Hydrochlorothiazide (HCTZ) was encapsulated using an aqueous wet granulation process with the use of two types of HPC: Klucel-EF

(produced by Hercules, USA) and HPC-L (made by Nippon Soda, Japan). Granulations made with various HPCs were comparable in compressibility and compatibility; however, Klucel-EF dissolved more quickly and had lower cloud point values. Molecular substitution and hydroxypropyl content were the two main factors that contributed to the observed property discrepancies. By creating a thinner coating surrounding HCTZ, Klucel-EF facilitates the drug's faster breakdown and release [20].

2.1.2 Hydroxypropyl Methyl Cellulose (HPMC)

HPMC has been employed in oral sustained-release pharmaceutical tablets since the early 1960s. Hydrophilic cellulose ethers, or HPMCs, have a polymeric structure and are soluble in water. Polymer chains are hydrated by surrounding water molecules when the drug is delivered via HPMC. This process will break down the HPMC matrix, allowing the active ingredients to be released [21]. The fact that two systems interact to determine drug release is well known: (1) permeation through the HPMC gel layer; (2) degradation of the HPMC matrix [22]. Most highly water-soluble drug release from an HPMC matrix is diffusional. Nearly insoluble drugs or low-viscosity HPMC coating agents may release drugs via matrix erosion processes [23]. The ratio of surface area to volume also plays an important role in controlling the release patterns of drugs from matrices based on high-performance microcapsules. An increased surface area-to-volume ratio would result in a more rapid drug release [24]. Anlar et al. documented compressing carbomer directly to form an HPMC-based interpolymer complex in acidic pH. Boccoadhesive controlled drug delivery verified non-Fickian morphine sulfate release [25]. A study conducted by Macleod et al. evaluated the way radiolabeled (99mTc) tablets coated with HPMC-pectin-chitosan film administer drugs to the colon. The pills showed signs of well-regulated administration, according to the results of the Gamma Scintigraphy study on gastrointestinal transit. The pills can pass through the digestive tract and start to dissolve in the colon [26].

2.1.3 Ethylcellulose (EC)

EC is a non-ionic ether of cellulose, rendering it insensitive to pH variations. It is insoluble in water but can dissolve in several chemical solvents [27]. When binders that are soluble in water are not sufficient, EC is frequently selected for drug delivery systems. One or more medications can be administered using it to prevent them from interacting with other compounds. Adding EC can decrease the oxidation of compounds like ascorbic acid that are easily oxidizable [28]. A coated layer for sustained drug release can be produced in drug delivery systems by integrating ethyl cellulose with water-soluble polymers. Ethylcellulose produces water-soluble hydroxyethyl cellulose (HEC), a non-ionic cellulose ether. It forms different viscosities and characteristics in water but is insoluble in organic solvents, forms a film, and

suspends medicinal tablets to restrict release, especially when a non-ionic chemical is desired [29]. Remuñán-López et al. detailed compressing EC-based bilayer composites that have been fabricated via a casting/solvent evaporation method. Mucoadhesive bilayers could have an anionic crosslinking polymer (polycarbophil, sodium alginate, gellan gum) in addition to a drug-chitosan composite layer and an ethyl cellulose backing layer. Nifedipine and propranolol hydrochloride are among the medications that can be delivered unidirectionally to the mucosa by use of the constructed bilayer structure [30]. The tablets prepared in a phosphate buffer at a pH of 6.4 demonstrated controlled swelling and an extended release of medication. A distinct study developed a laminated double-layer film by merging a drug-infused layer with a drug-free membrane made from ethyl cellulose (EC), hydroxypropyl cellulose (HPC), and various polyethylene glycol (PEG) formulations. The thickness significantly influenced the rate constants for drug release from the drug-free EC-based membrane, with the *in vitro* drug release profile adhering to zero-order kinetics [31]. Bussemer et al. effectively created an electrical current-based pulsatile medication delivery system that is defined by rapid release after a predetermined delay. A protective layer was created by effectively spray-coating an EC-ethanol emulsion over the drug-filled hard gelatin capsule, which would subsequently be encased in a robust polymeric coating. To achieve continuous medicine release, one can alter the duration of the lag by adjusting the swelling layer hydration capacity and the formulation of the polymeric coating [32].

2.1.4 Methylcellulose (MC)

MC generates a transparent to opalescent, thick solution when mixed with water [33]. Since polar hydroxyl groups are inhibited, MC high degree of substitution (DS) may reduce its solubility. Since it is not absorbed by the intestines, MC solutions remain stable across a wide pH range (2 to 12) without major changes in viscosity. Diverticulosis, constipation, ophthalmic formulations, and burn ointments are just a few of the many areas where this finds widespread use. For medications with poor water solubility, MC has long been recognized for its capacity to enhance solubility and bioavailability when utilized as a carrier [34]. However, it was also pointed out that if you take too much MC, you could end up with a blocked intestine. The many hydroxyl groups in MC interact with the carboxylic acid of carboxyvinyl polymer [35]. Ozeki et al. reported that MC-CP solid dispersion granules that release antipyretic phenacetin. [36]. A 50:50 ratio yields the lowest release; however, the MC/CP ratio determines the release profile. At this MC/CP ratio, PHE release declined until it stabilized at 180,000 g/mol as MC molecular weight grew. El-Kamel increased the viscosity of timolol maleate formulations with MC, reducing dosage and prolonging TM administration, mitigating Pluronic F127 (PF127) harmful effects [37]. Formulations with 15% PF127 and 3% MC (PF127-MC) release drugs gradually best. Compared to the control group receiving 0.5% TM solution, PF127-MC increased TM ocular bioavailability 2.4-fold in albino rabbits. In PF127, MC can form a more resilient TM release

barrier. Kumar et al. developed an MC-Carbopol® situ-forming ophthalmic Medication Delivery System [38]. A yield point and pseudoplastic behavior were discovered during the rheological examination of this system. The yield point, shear stress, and viscosity would all increase with an increase in the dosage of MC or Carbopol®. Using a low-viscosity gel made by adding 1.5% MC to 0.3% carbopol®, one can create a drug-containing liquid with reversible phase transitions and an extended residence duration in the delivery system. The MC-containing medicine may only exert its impact along its route to the target if it is released consistently. For example, Gavini et al. found that Chitosan microspheres that were loaded with medication and had MC (Metolose) as an additional excipient did not exhibit regulated release behavior in vitro when it comes to the local dispersion of acriflavine [39].

2.1.5 Sodium Carboxymethyl Cellulose (CMC)

Carboxymethylation, which is a normal etherification reaction, is responsible for the transformation of cellulose into sodium carboxymethyl cellulose (CMC) [40]. Sustained drug release can be achieved with the help of this inexpensive polyanionic excipient and soluble cellulose derivative [41]. This polymer has numerous applications due to its exceptional qualities, which include stabilizing, suspending, binding, and thickening. The most suitable CMC grade for disintegration is one that has been heavily polymerized and has few carboxymethyl groups [42]. Ineffective disintegration agents are grades with a low degree of polymerization, regardless of the amount of substitution. When applied chemically, methyl chloride (CMC) inhibits the over cleavage of the superoxide dismutase (SOD) enzyme, which has medicinal applications [43]. Hydrogels made with CMC can carry SOD, allowing for its continual release. The addition of SOD to CMC matrix forms hydrogels and conjugates. Both formulations released half the SOD after 72 h, indicating a more controlled release profile [44]. Barkhordari et al. synthesised novel pH-sensitive nanocomposite beads based on CMC by integrating CMC with layered double hydroxides (LDH) [45]. Coprecipitation was used to intercalate Ibuprofen (IBU) with the CMC-LDH bead. In vitro drug delivery assays reveal that CMC-LDH-IBU nanohybrids protect IBU from gastric pH and release it in the gut. According to Krishna et al., a transdermal method using CMC lowers the first-pass metabolism of the β -adrenoceptor antagonist Propranolol, which is typically administered orally. Permeation tests on hairless rat skin models revealed a drug penetration rate of $52.87 \pm 11.63 \mu\text{g}/\text{cm}^2/\text{h}$ after 24 h in a modified Franz diffusion cell [46].

3 Mechanisms of Drug Loading and Release

To ensure stability, bioavailability, and therapeutic effectiveness, cellulose-based drug delivery systems employ multiple means of loading and releasing peptides and proteins Fig. 2 [10]. The factors that determine the ideal drug loading method and

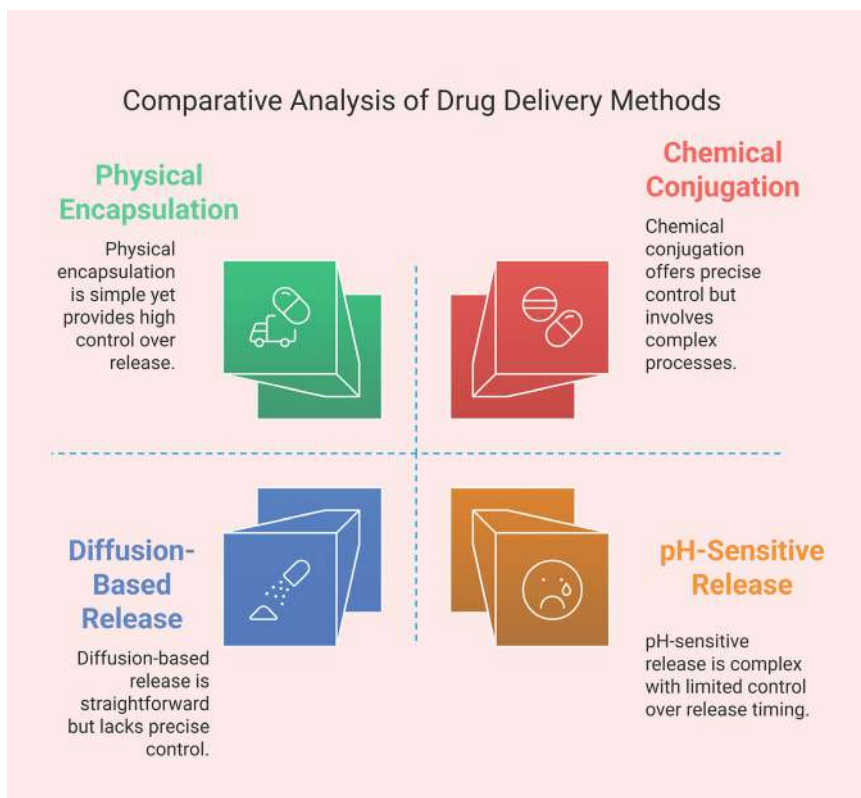


Fig. 2 Comparative analysis of drug delivery methods

release configuration include the physicochemical properties of the medicinal agent, the target release profile, and the desired biological environment [11]. There are two basic ways that peptides and proteins can be loaded into cellulose-based carriers: chemical conjugation and physical encapsulation. Regulated release of the loaded biomolecules can be made possible through hydrogel swelling, enzyme-triggered schemes of degradation, pH sensitivity, and diffusion. All these approaches have their respective advantages in optimizing drug stability and targeted delivery to achieve controlled long-term therapeutic effects [11].

3.1 *Physical Encapsulation Versus Chemical Conjugation*

The method of delivery of proteins or peptides into cellulose carriers is physical encapsulation [47]. Weak adhesion mechanisms include hydrogen bonding, electrostatic forces, and van der Waals interactions that keep biomolecules stuck inside

a polymeric matrix. Encapsulation methods include solvent evaporation, freeze-drying, electrospinning, and nanoprecipitation [48]. Benefits accrue from physical encapsulation since it does not chemically change the drug but preserves structural integrity and bioactivity. Major characteristics that determine drug loading and release efficiency are hydrophilicity, swelling, and porosity of the cellulose-based carrier. Ideal for sustained-release formulations, physical encapsulation permits slow release of the drug from the polymeric network, providing long-term therapeutic effects. Environmental conditions sometimes compromise encapsulated protein and peptide stability in terms of pH and temperature fluctuations, which may lead to short-term action and destruction of drugs despite their merits [49]. Chemical conjugation can also be carried out by chemically bonding proteins or peptides to cellulose derivatives using chemical linkers [50]. It provides several advantages, such as enhancing stability, enabling targeted distribution, and regulating the release through stimulus-responsive mechanisms. The introduction of hydroxyl, carboxylic, and amine groups on cellulose derivatives creates an opportunity for the formation of covalent interactions with biomolecules [51]. Esterification, amidation, and click chemistry are other common approaches for chemical conjugation with the desired level of control over the release and drug attachment [52]. The cross-linking of the drug is one of the main advantages of chemical conjugation, as the drug is sheltered from entering an early phase of release and is thus well protected against enzymes from degrading proteins or peptides. Temperature, pH, enzyme activity, and other physiological variables can induce drug release with stimuli-responsive linkers. However, meticulous optimization is a must; many times, chemical conjugation might involve a complicated fermentation process and could also alter the biological activity of the drug Table 1 [53].

3.2 *Diffusion-Based Drug Release*

The majority of cellulose-based drug delivery devices use diffusion control to release drugs [60]. The drug molecules diffuse out of the polymeric carrier to the environment, releasing the encapsulated proteins or peptides. The porosity of the polymer matrix, the gradient of drug concentration, and the physicochemical properties of the medicinal molecule are the parameters that dictate the rate of diffusion [60]. There are two types of diffusion-based release: Fickian and non-Fickian. The diffusion of drugs according to Fickian rules is toward the low concentration zone, and it occurs in a predictable fashion, which is classical diffusion according to equations of different types [60]. Non-Fickian diffusion happens in other effluents from swelling degradation or interactions with biological fluids, as far as drug release is concerned [61]. The cellulose-based carriers, including hydrogels and nanofibers, are best for diffusion-controlled release due to the retention of water and variation in the porosity. The researchers have given modifications like polymer composition, pore size, and crosslinking degree for making controlled or sustained release of drugs. The diffusion-based mechanism is very beneficial for long-lasting protein therapy as

Table 1 Advanced drug release strategies from cellulose carriers: mechanisms and their implication

Mechanism	Description	Advantages	Disadvantages
Physical encapsulation	A polymeric matrix traps biomolecules via weak interactions (van der Waals, electrostatic forces, hydrogen bonds). Solvent evaporation, freeze-drying, electrospinning, nanoprecipitation	Maintains drug structural integrity and bioactivity – Suitable for sustained-release formulations	Stability issues under environmental fluctuations (pH, temperature) – Risk of short-term action and premature drug degradation [54]
Chemical conjugation	Proteins/peptides are chemically bonded to cellulose derivatives using linkers. Techniques: esterification, amidation, click chemistry	Enhances drug stability and targeted delivery Enables stimuli-responsive release (pH, temperature, enzyme activity) – Prevents premature drug degradation	Complex synthesis process – Potential alteration of drug bioactivity [55]
Diffusion-based release	Drug molecules diffuse out of the polymeric carrier, with the release rate determined by polymer porosity, drug concentration gradient, and drug properties. Can be Fickian (predictable) or Non-Fickian (influenced by swelling/degradation)	Suitable for long-term protein therapy – Maintains drug concentration in the bloodstream	– Risk of burst release leading to initial high drug concentration and reduced long-term effectiveness [56]
pH-sensitive release	Utilizes pH-sensitive cellulose derivatives (e.g., CMC, HPMC) to control drug release based on pH variations. Compact at low pH (stomach) and swells at higher pH (intestines, tumor microenvironment)	Targeted drug release in the gastrointestinal tract or tumor sites – Protects drugs from gastric degradation	– May require combination with other methods (e.g., hydrogels) for precise control [57]

(continued)

Table 1 (continued)

Mechanism	Description	Advantages	Disadvantages
Enzyme-triggered degradation	Drug release occurs due to enzyme-mediated degradation of cellulose carriers (e.g., cellulase, protease, MMPs)	Site-specific drug release with minimal systemic side effects – Prevents premature drug breakdown, enhancing therapeutic efficacy	– Requires careful control over polymer composition to match enzyme activity at target site [58]
Hydrogel-based swelling-controlled release	Swelling of cellulose-based hydrogels in biological fluids enables drug diffusion through hydrogel channels. Release kinetics are controlled by polymer composition, crosslink density, and functional group interactions	Sustained and predictable drug release Prevents protein denaturation and aggregation – Responsive to physiological signals (temperature, pH, ionic strength)	– May require a combination with enzymatic degradation or pH sensitivity for improved control [59]

it preserves medication concentration in the blood, which is important for achieving the best possible therapeutic effects. However, one of the disadvantages of this is the implementation of burst release, in which a large quantity of drug is released immediately after administration, followed by a substantial change in concentrations and reduced effectiveness of the drug. There are still other modifications such as surface coatings, polymer blends, and nanoparticle encapsulation, which would control the diffusion rates and promote the retention of drugs that need to be tackled [62].

3.3 *pH-Sensitive Drug Release*

pH-sensitive drug release mechanisms exploit the pH-sensitive characteristics of cellulose derivatives for targeted and controlled delivery of drugs. It works wonders in oral and tumor-targeted drug delivery, considering that the physiological pH changes serve as stimulus signals for the drug release at the site of action. CMC and HPMC react differentially to tissue pH variations in swelling and solubility. Hence, they are ideal candidates for pH-responsive drug carriers [63]. The carriers on the pH-sensitive cellulose remain compact and unswollen in acidic environments like the stomach (pH 1.2–3.0), delaying the release of drugs. When the pH increases as in the gut intestines (pH 6.5–7.5) or in the tumor microenvironment (which in most cases is slightly acidic), the polymeric network swells and initiates the release of encapsulated proteins and peptides [64]. This tailored release method enhances drug

bioavailability while minimizing degradation and off-target effects. Although several studies researched pH-sensitive release mechanisms for the stability of peptide-based drugs like insulin and vaccines against gastro-degradation during oral delivery, this technique can also be combined with other controlled-release techniques, such as hydrogel swelling and enzymatic breakdown, to improve precision in drug delivery [65].

3.4 Enzyme-Triggered Degradation

Enzyme-triggered drug release intends to achieve controlled and selective release of drugs in the enzymatic environment existing in the body. This is of great importance for cellulose carriers since these can be designed to degrade in the presence of enzymes at the desired site. For example, cellulase enzymes could aid the controlled release of drugs by the dissolution of cellulose into smaller sugar units. The researchers can manipulate the degradation rate of cellulose carriers for sustained and site-specific drug delivery by managing the degree of polymerization and including enzyme-sensitive linkages [66]. Enzyme-responsive drug-delivery devices are excellent for protein and peptide therapies because they possess specific drug release patterns with little or no systemic side effects. For example, cellulose-based carriers can be constructed for directed degradation by matrix metalloproteinases (MMPs), which are responsible for overproduction in tumor tissues, in applications such as cancer therapy. Just like in drug delivery systems for gastrointestinal applications, protease-sensitive cellulose derivatives could be used to shield therapeutic peptides from stomach degradation and release into the intestines. Such an approach ensures better stability and therapeutic efficacy as the medicine gets to its action site with minimal losses [67].

3.5 Hydrogel-Based Swelling-Controlled Release

The swelling property of cellulose-based hydrogels causes the release of drugs from drug delivery systems. The hydrogels maintain their structural integrity amidst high water content in three-dimensional polymeric networks. When in biological fluids, the hydrogel swells, allowing drugs to diffuse and be released from the channels created. Adjusting the swelling level, polymer composition, and crosslink density affects the medication release kinetics [68]. The continuous and predictable profile of drug release with the drug swelling-controlled release mechanisms makes it the most suitable dosage form for the long-term delivery of proteins and peptides. These hydrogels can react to physiological signals like temperature, ionic strength, and pH, making them useful for medication administration. One more advantage associated with hydrogels is that they create a barrier through which encapsulated proteins do not denature or clump together. Further, if the swelling-controlled release is coupled with

some other method, such as enzymatic breakdown or pH responsiveness, that may bring promising advances in hydrogel-based carriers for targeted and individualized therapy [69].

4 Applications in Protein and Peptide Drug Delivery

Developing efficient methods of medicine administration is crucial for proteins and peptides due to their rapid enzymatic degradation, low bioavailability, and swift clearance from the body. Morphological and functional polymeric carriers from cellulose can enhance the bioavailability and controlled-release characteristics when appropriately formulated to stabilize these drugs for delivery through various routes. Various routes of drug delivery have been studied via cellulose and its derivatives, including oral, injection, transdermal, mucosal, and stimuli-responsive drug delivery, based on the target site and therapeutic need. Each route has its advantages when it comes to the efficient delivery of the protein or peptide with minimal degradation and unwanted effects [70].

4.1 Oral Delivery (*Protection from Enzymatic Degradation, Intestinal Absorption*)

The epoch of drugs delivered through the oral route has not been challenged due to its low price, easy patient handling, and relative ease of administration. Still, many hurdles oppose the oral delivery of protein and peptide drugs; these hurdles are mainly the enzymatic destruction of the drug in the gastrointestinal tract and low intestinal permeability. These biomolecules are digested within the stomach due to the acidic pH by the enzymes of digestion of pepsin, trypsin, and chymotrypsin, into monomers, which are then hardly absorbed into the bloodstream. Tight junctions in the intestinal epithelium severely limit the entry of large hydrophilic molecules such as peptides and proteins, so their oral bioavailability is decreased significantly [71]. To solve all these problems, significant research has been done on cellulose-based drug delivery systems. It forms protective matrix types around the protein and peptide drugs, thereby preventing their degradation by enzymatic means. They include carboxymethyl cellulose, hydroxypropyl MC, and cellulose nanocrystals. Incorporating these cellulose derivatives into enteric-coated formulations allows the medicine to be delayed until it reaches less acidic intestinal sites. Proteins and peptides are protected until they reach the best absorption site due to the pH-sensitive swelling characteristics of particular cellulose derivatives, which enable site-specific release. Hydrogels and cellulose nanoparticles also improve absorption in the intestines, making it difficult for drugs to diffuse through the epithelium [72]. Mucoadhesive cellulose derivatives have been researched in drug absorption-oriented

research to enhance bioavailability and retention of drug action by maintaining the medicine in the lining of the intestine for a longer time. Functional excipients such as enzyme inhibitors and permeability enhancers in cellulose-based oral delivery techniques have the potential as means of enhance systemic availability and stability of peptide and protein therapies [73].

4.2 Injectable Systems (Nanoparticles, Hydrogels for Sustained Release)

High bioavailability means avoiding enzymatic degradation and bypassing the gastrointestinal tract, and hence, most injectable systems for drug delivery are employed for proteins and peptides. However, therapeutic concentrations are hard to maintain owing to rapid systemic clearance, thus creating great hurdles. Sustained drug release from a controlled release formulation incorporating cellulose-based carriers is an efficient solution to these limitations in the current use of drugs [74]. Protein and peptide injectable delivery using cellulose nanoparticles has been the subject of substantial investigation. Cellulose nanocrystals (CNCs) and cellulose nanofibers (CNFs) are sources of nanoparticles with a very high surface area for adsorption and retaining drugs from loss through enzymatic degradation. Such targeted therapy can be accomplished by attaching specific ligands to the nanocarriers. Accordingly, one would be able to achieve organ- or tissue-specific targeting for the drug. Again, surface modification with hydrophilic polymers, like polyethylene glycol, could help improve circulation time due to decreased clearance over the reticuloendothelial system [75]. There has been a lot of buzz around the development of injectable hydrogel formulations for longer peptide and protein drug delivery. Highly porous three-dimensional networks offered via cellulose hydrogels enable the encapsulation of biomolecules as well as regulated drug diffusion. More crosslinked structures, which have drug release at sustained, prolonged rates, determine the kinetics of release in these hydrogels in terms of the degree of crosslinking. MC and other thermosensitive cellulose derivatives change from sol to gel through temperatures reaching the body temperature, providing in-situ formed hydrogels whenever injected. This characteristic is very useful in the targeted delivery of medicines for the reason that hydrogel remains at the injection site. Therefore, for such systems, research efforts have been focused on improving patient compliance and reducing injection frequencies for long-term delivery of growth hormones, insulins, and monoclonal antibodies [76].

4.3 *Transdermal and Mucosal Delivery (Films, Patches, Buccal Delivery)*

Non-invasive drug administration includes new alternative routes, entailing transdermal and mucosal pathways, which will enhance patient adherence and allow for very controlled release of the drug into the body. However, proteins and peptides are highly hydrophilic molecules with a great molecular dimension that makes it impossible for them to cross biological barriers such as the stratum corneum in the skin or the mucosal epithelium within the mouth and nose when administered through these pathways. Various approaches have exploited different cellulose-based polymers to enhance transdermal and mucosal delivery of peptide and protein medications by improving permeability and stability [77]. Cellulose-based films and patches serve as carriers for peptide and protein-mediated transdermal delivery. Biomolecules can perforate through the skin barrier at a controlled rate via hydroxypropyl cellulose-thin-film matrices (HPC) and MC (MC). In the presence of cellulose adhesive polymers, the retention of drugs can be prolonged due to increased skin contact. Microneedles are another candidate for enhancing transdermal permeability by establishing microchannels through the skin to enable the transport of proteins and peptides with minimal pain and discomfort [78]. Lately, these alternative modes of administration have become more attractive for enhancing systemic absorption and bypassing the action of enzymes: buccal and sublingual. Hydrogels and films made from cellulose disintegrate in the buccal and sublingual mucosa, depending on the thickness of the polymeric wall, and different hydrogels differ in their drug release properties. Good CMC and HPMC are mucoadhesive, so they will increase the length of time of retention, which means the drug can be absorbed over a longer period. Cellulose-based polymeric nanoparticle formulations and nasal sprays are further two approaches developed for enhancing the transport of peptide drugs across the nasal epithelium, thereby taking advantage of the abundant vascularization of the nasal cavity for quick systemic effects Table 2. Vaccines, peptide-based hormone therapies, and medications targeting the CNS have massively benefited from these exploits [79].

4.4 *Stimuli-Responsive Delivery (pH, Temperature, Ionic Strength)*

Stimuli-responsive drug delivery systems have made much advancement in protein- and peptide-based therapies. These innovations make it possible to precisely control the release of drugs in reaction to predetermined physiological signals. A wide variety of cellulose-based polymers have been developed for targeted drug administration, based on their ability to respond to temperature changes, ionic strength, and pH [64]. Such cellulose carriers that respond to the pH changes are based on polymers which swell or degrade on exposure to a certain pH, and therefore allow delivering the

Table 2 Cellulose-based strategies for overcoming challenges in protein and peptide drug delivery

Delivery route	Challenges in protein/peptide delivery	Cellulose-based strategy	Advantages
Oral delivery	Enzymatic degradation in the GI tract – Poor intestinal permeability	Enteric-coated cellulose formulations (CMC, HPMC) to protect against stomach acid pH-sensitive swelling properties for targeted intestinal release – Mucoadhesive cellulose derivatives for prolonged retention and absorption	Enhances protein stability Improves absorption in the intestine – Increases bioavailability [65]
Injectable systems	Rapid systemic clearance – Frequent dosing required	Cellulose nanoparticles (CNCs, CNFs) for targeted and prolonged circulation PEG-functionalized cellulose carriers to enhance half-life – Hydrogel-based sustained release (MC, crosslinked cellulose)	Avoids GI degradation Ensures controlled release over time – Improves patient compliance with reduced dosing frequency [64]
Transdermal delivery	Poor permeability across the skin barrier – Low absorption efficiency	Cellulose-based films and patches (HPC, MC) for controlled release – Microneedle-assisted cellulose formulations to enhance permeability	Non-invasive alternative to injections Provides prolonged drug release – Reduces systemic side effects [80]
Mucosal delivery	Rapid drug clearance from mucosal surfaces – Low absorption through epithelial barriers	Mucoadhesive cellulose hydrogels (CMC, HPMC) for prolonged retention – Cellulose-based nasal sprays and nanoparticles for enhanced transport	Avoids first-pass metabolism Ensures faster systemic absorption – Suitable for CNS-targeted delivery (nasal route) [81]
Stimuli-responsive delivery	Need for controlled and targeted release – Risk of premature drug degradation	pH-sensitive cellulose carriers for site-specific release (CMC, HPMC) Temperature-sensitive MC hydrogels for localized sustained delivery – Ionic strength-responsive cellulose carriers for precise dose control	Ensures targeted and controlled release Minimizes off-target effects – Enhances drug efficacy and safety [82]

desired medication at targeted locations. For example, when entered into the stomach, formulations containing CMC or HPMC remain stable. However, when they reach the intestinal tract, where the pH is more neutral, they swell and release the medicine. This method becomes much more useful for oral protein delivery, it ensures that the therapeutic biomolecule reaches its site of absorption intact. Methylcellulose (MC) and other temperature-sensitive cellulose derivatives can release drugs in a controlled manner due to their reversible sol–gel transitions. Injectable hydrogels from MC become liquid at room temperature, but upon injection, turn into a gel-matrix which causes the medicine to be released slowly but surely from the location of injection. These thermoresponsive devices have been utilized widely by tissue engineers to deliver growth factors and other regenerative proteins to specific locations [83]. When the ionic strength varies, bio-responsive cellulose carriers become able to release drugs by utilizing physiological variations in the concentration of ions. By varying the ionic strength, while disrupting the electrostatic association of charged biomolecules and cellulose-based carriers, drug molecules can disassociate from the carriers in a controlled manner. This method is specifically useful for therapeutic proteins and peptides that need finely tuned dose adjustments according to the user's physiological condition [9]. Protein-peptide therapies can be delivered with high efficiency and precision via cellulose-based drug delivery devices that exploit the above-mentioned stimuli-responsive properties. The prospects for improved drug stability, reduced side effects, and enhanced therapeutic outcomes will be greatly improved by the design of materials that respond to specific biological cues [84].

5 Challenges and Limitations

Although they provide a plethora of advantages, cellulose-based drug delivery systems for proteins and peptides still have some hurdles to overcome before they are applied extensively in clinical settings. Two major issues are addressing the safety and efficacy of protein therapies while negotiating the rather complicated regulatory landscape that is known to exist. Another important point in this regard is the increase in the production of cellulose-based formulations for commercial use. All these involve extensive safety evaluation along with scalable production methods and innovative formulation strategies. All these barriers will have to be overcome for cellulose-based carriers to join the mainstream of biopharmaceutical applications.

5.1 Protein Stability and Bioactivity Retention

One of the main challenges in delivering a protein or peptide-based medicine is maintaining bioactivity and stability during preparation, storage, and administration. Various mechanical stress conditions, changes in pH, and temperature shifts severely affect proteins and peptides. During formulation and encapsulation, and

storage, proteins may experience denaturation, aggregation, or degradation, leading to the loss of therapeutic efficacy. While cellulose and its derivatives help stabilize these molecules, there are challenges in storing them for prolonged periods [85]. The binding of protein to the carrier matrix is a major impediment to cellulose-based delivery of medicine. The binding of proteins to cellulose surfaces can cause changes in structure and can be strong enough to render some biological activity useless. The rate of release of proteins from cellulose-based carriers has to be carefully managed to prevent too early degradation [86]. Any over-slow or over-rapid releases will hurt several proteins, which survive on the delicate balance of hydration and structure. This situation led the scientists to search for surface-modification techniques of cellulose carriers to lessen nonspecific protein binding and thus enhance their stability. Storage and delivery of proteins can be improved under protective excipients like sugars, amino acids and surfactants [87]. Moreover, the enzymatic degradation of drugs is a recent concern. Proteases in the biological environment would also degrade a protein drug before it reaches the target site of action. Carriers based on cellulose would need to be engineered to protect proteins from degradation by enzymes, but have a mechanism of controlled release at the target site. Very promising innovations have emerged to face these challenges by using the methods of nanoencapsulation, hydrogel formulations, and crosslinked cellulose networks; however, fine-tuning is still required for targeted protein therapies in this area. Before administration, reconstitution has been thought to yield added long-term stability, and lyophilized cellulose-protein formulations have also been discussed [88].

5.2 *Scaling up Cellulose-Based Formulations*

Cellulose materials for drug delivery have some advantages, but their cheap production and massive production have still, so far, been a prominent issue. Enhancement, cost-effectiveness, and reproducibility of processing methods have been paramount in bridging laboratory-scale synthesis and industrial-scale manufacture. A critical concern is that consistency with regards to the physicochemical properties of such cellulose-based carriers can directly affect drug loading efficiency and release kinetics if there are even slight changes in the polymer structure, degree of substitution, and particle size [89]. Carbon nanocrystals (CNCs), carboxymethyl cellulose (CMC), and HPC are a few examples of cellulose derivatives that can be modified chemically to produce structures with a high degree of homogeneity. These processes need to be scalable up to manufacturing levels to be capable of delivering consistent batch-to-batch reproducibility without necessarily compromising the functional properties of the drug delivery system. For instance, CNCs typically derive from plant-based cellulose and are hydrolyzed in acid. However, different source substrate plants can cause differences in their surface charge, particle size, or crystallinity. To achieve repeatable performance in drug delivery, standardization of such characteristics has to be done [90]. It is not just the machining and drying methods that hinder the scale-up of cellulose-based medicines. Spray-drying or freeze-drying is

required to preserve the structure of many cellulose-based systems, including hydrogels and nanocarriers. For mass production, these methods are not always the cost-efficient route considering their energy and time expenditure. Thus, for commercial viability, more efficient drying and processing methods will need to be developed for cellulose-based drug carriers [90]. In addition, challenges remain about logistics for the integration of cellulose-based drug delivery systems into existing pharmaceutical manufacturing pipelines. Biopolymer-based carriers require a reconfiguration of existing machinery and knowledge traditionally meant to address small molecules in the area of medication packing and formulation. Hence, to facilitate the commercialization and ease the manufacturing of cellulose-based medicine formulations, collaboration should occur amongst pharmaceutical companies, materials scientists, and regulatory bodies [91].

5.3 Regulatory Concerns and Safety Considerations

The regulatory approval process for cellulose-based drug delivery systems presents another significant hurdle in their widespread adoption. To determine whether a new medication delivery platform is safe, effective, and stable, regulatory bodies like the FDA and the EMA conduct comprehensive preclinical and clinical trials. However, GRAS has determined that cellulose and its derivatives are safe for human consumption by regulatory bodies; their use in advanced drug delivery applications, particularly for proteins and peptides, requires thorough evaluation. Immunogenicity that may arise from cellulose-based carriers constitutes one of the main regulatory issues. Whereas cellulose itself is safe and nontoxic, some derivatives may react immunologically due to impurities or alteration. Depending on the example, in the biocompatibility context, one should ensure that any remnants of derivatization chemicals, such as organic solvents or cellulose modification reagents, are eliminated. Cellulose-based formulations are clinically cleared only after rigorous quality control assessments of endotoxin levels, sterility, and purity [92]. The *in vivo* breakdown profile of cellulose-based carriers is yet another parameter to assess safety. Indeed, the breakdown in the body differs from that of other cellulose-based carriers; for example, it depends on polymer constructs and method of production. What is more worrying is the possibility of the slow or partial breakdown causing the accumulation of cellulose-based compounds in tissues over prolonged periods. This raises safety questions. Extensive degradation assessments are specifically required by regulatory agencies when it comes to implanted and injectable drug delivery systems investigation including biocompatibility and elimination routes with cellulose carriers, further checks [90]. Regulatory scrutiny of protein and peptide medicine is indeed very high, given their inherently complex nature. The protein therapeutics require interacting with the cellulose carriers for stable biological activity, controlled release kinetics, and long-term stability, such interactions must be studied. Regulatory bodies necessitate careful analysis of the encapsulated proteins' stability during formulation,

including spectroscopic, chromatographic, and biological assay studies [90]. Regulatory agencies impose demanding requirements for the scalability and reproducibility of cellulose-based drug delivery systems, and these systems are subjected to preclinical and clinical testing. Quality control for each of the production runs is performed under good manufacturing practice regulations. To obtain regulatory approval for cellulose-based formulations, defined production methods must be established and reproducibility demonstrated. The collaboration efforts of researchers, pharmaceutical industries, and regulatory authorities will be required to cross the hurdles posed by regulations concerning cellulose-based drug delivery systems. To ensure early licensing and compliance with safety standards, it is beneficial to include the regulatory authorities in the drug development process from the beginning. Advances in analytical techniques, in vivo evaluation models, and quality control methodologies will greatly aid in overcoming regulatory hurdles as well as effective translation of cellulose drug carriers into clinical practice [9].

6 Future Perspectives

Great advances have taken place in the material changes, methods of fabrication, and their therapeutic applications, driving the field of cellulose-based drug delivery for proteins and peptides at an accelerated pace Fig. 3 [91]. Future research works will improve drug stability, controlled release, and targeted delivery by overcoming the existing challenges and augmenting the functional abilities of cellulose-based carriers. Smart modifications of cellulose, Novel methods to medication delivery of peptides and proteins include 3D printing of cellulose scaffolds and combination treatments. Such innovations enhance therapeutic efficiency and will soon usher in patient-centered treatment modalities in personalized and precision medicine approaches [93].

6.1 *Advanced Cellulose Modifications (Smart and Functionalized Materials)*

The innovative fabrication of smart and functionalized cellulose materials that can respond to specific environmental or biological signals marks one of the most exciting developments in cellulose-based drug delivery. In themselves, traditional cellulose derivatives are already very effective in drug loading and release, but once further functionalized, these materials would lend themselves to controlled and targeted delivery of proteins and peptides. Nowadays, new studies are focusing on the incorporation of pH, temperature, and enzyme-sensitive groups onto cellulose to finely tune drug release in response to physiological parameters [9]. From the viewpoint of site-specific delivery of therapeutics, one example could be the targeted release

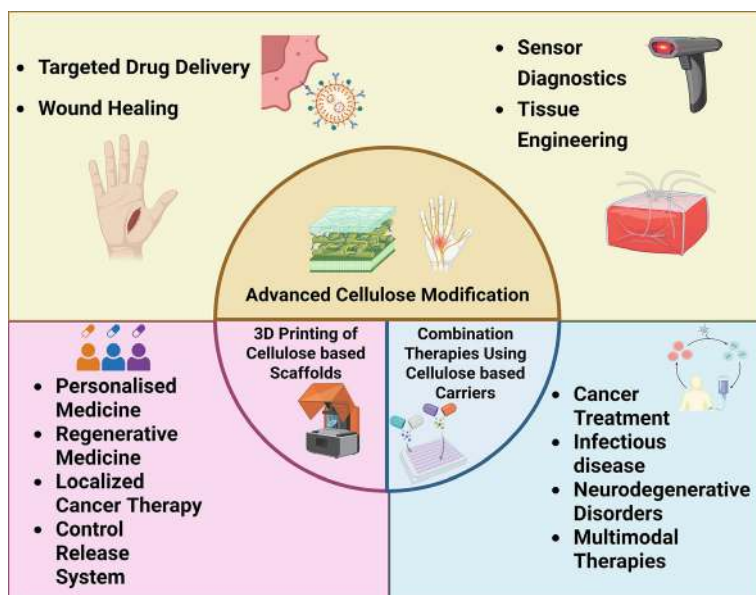


Fig. 3 Future perspective of cellulose-based protein and peptide

of proteins in the intestines or tumor microenvironments through the action of pH-sensitive cellulose derivatives. Whenever the polysaccharides carboxymethyl cellulose and hydroxypropyl MC are pH-responsive, they will protect therapeutic proteins from acidic conditions while allowing for swelling and payload release in neutral or alkaline conditions. In this manner, protein therapeutics are delivered intact through the stomach and then released when they reach their site of absorption. Enzyme-responsive cellulose carriers are also built to disintegrate and release their therapeutic payload in the presence of specific enzymes found in diseased tissues. These biomaterials are of immense value for cancer therapy, whereby cellulose hydrogels sensitive to matrix metalloproteinases can precisely deliver therapeutic peptides into tumor tissues [94]. In addition to responsive behavior, the conditioned distribution of proteins or peptides has been achieved, using bioactive ligands coupled to cellulose-based carriers. Drug-carrier mechanisms have been developed that enable specific binding to target cells with minimal off-target effects through the conjugation of cellulose derivatives with antibodies, peptides, or aptamers. Improvement of drug absorption and internal delivery is then made possible by designing molecular affinity cellulose nanofibers and nanoparticles to bind to specific cell surface receptors. This method finds its strongest applications in regenerative medicine and cancer therapy, where peptide-based medicines, monoclonal antibodies, and growth factors can be delivered specifically [95]. Another promising and exciting development in smart cellulose material is the inclusion of magnetic and electrically responsive cellulose derivatives. One interesting and non-invasive alternative for targeted, specific

protein delivery is the directional external guidance of magnetic cellulose nanoparticles using magnetic fields. The release rates of protein drugs can be dynamically controlled using electrically conductive cellulose hydrogels, among others. Electric stimulation has also been studied for controlled release. Such advancements would certainly add to the robustness and precision that cellulose-based systems provide in customized, patient-specific delivery systems [96].

6.2 3D Printing of Cellulose-Based Scaffolds for Personalized Protein Delivery

The rise of 3D printing has opened up new possibilities for the manufacture of cellulose-based scaffolds for the targeted distribution of pharmaceuticals. Instead of using a generic, one-size-fits-all approach like the previous technique of medicine distribution, 3D printing allows for the customization of drug carriers to meet the individual needs of each patient. Thus, researchers can develop highly efficient and individualized systems for delivering proteins and peptides employing the modified designs of scaffold architecture, porosity, and drug distribution of cellulose-based scaffolds [97]. A wide range of cellulose derivatives, such as hydroxypropyl MC, MC, and bacterial cellulose, can all be combined into bioinks compatible with the process of additive manufacturing. Scaffolds made out of cellulose, therefore, can be directly into 3D printing. These bio-inks can print intricate, multilayered architectures with controlled drug release so that therapeutic proteins can be delivered on demand. This is especially useful due to the critical importance of scaffold-based protein delivery in regenerative medicine applications related to tissue repair and regeneration [98]. In addition, three-dimensional 3D printing provides the possibility to design multi-drug delivery systems that can incorporate various peptide and protein therapies into distinct scaffold layers. This facilitates sequential or combination therapy approaches. For example, a cellulose scaffold may have two layers: one for the rapid release of peptides to reduce inflammation, and the other for a slow yet sustained release of proteins to aid in tissue repair. This level of control over the drug release rate is very useful when considering neurodegeneration disorders, chronic wounds, and bone defects, which all require different therapeutic components at different times along the healing continuum. 3D printing and advancements in bioprinting technologies stand to benefit personalized medicine tremendously. This approach, by improving the efficacy of peptide and protein therapies and reducing the likelihood of immunologic rejection, enhances clinical outcomes [99].

6.3 *Combination Therapies Using Cellulose-Based Carriers*

Diseases like cancers, autoimmune diseases, and neurodegenerative disorders have all drawn attention towards the concept of combination therapy: simultaneous administration of more than one drug for synergistic therapeutic benefits. Cellulose-based carriers provide an ideal platform to this end for allowing co-encapsulation and regulated release of several protein and peptide medications [100]. The greatest benefit of synchronized release profiles of combination therapies is that they deliver cellulose-based combinations to target areas at appropriate concentrations and times. An example would be a start-releasing hydrogel, which can initially liberate an immunomodulatory peptide, followed by a continuous release of a monoclonal antibody to target tumor sites, for use in cancer treatment. This enables the maximization of therapeutic efficiency with minimal added risk for both toxicity and resistance development [101]. Combination therapies commonly face solubility challenges. However, development is feasible for cellulose-based carriers with the capability of delivering hydrophobic and hydrophilic drugs. The researchers conceived multi-drug delivery systems via cellulose nanoparticles or nanofibers with customized surface chemistry. These systems encapsulated hydrophilic peptides within a cellulose matrix while adsorbing onto the surface hydrophobic small-molecule medicines. By this dual-drug encapsulation strategy, both drug candidates' stability and bioavailability get boosted, and more synergistic treatment outcomes ensue [102]. Another opportunity for this combined therapy using cellulose-based carriers is in vaccine development. Nowadays, there are vaccines that not only consist of multiple antigenic proteins but also adjuvants administered at the same time to elicit very strong and long-lasting immune responses. Hydrogels and cellulose-based microparticles have been the focus of vaccine-delivery platforms. These could enhance immune activation by being formulated to co-encapsulate antigens along with immunostimulatory peptides. The possible improvements provided by this approach include enhanced stability of antigens, prolonged immunological exposure, and targeted delivery to cells that present these antigens, which could lead to more efficacious vaccination formulations [103]. By leveraging the special characteristics of cellulose-based materials, combination therapy modalities can be fine-tuned to obtain maximal pharmacological synergy, minimize adverse effects, and optimize therapeutic effectiveness. Next-generation personalized and precision medicines will be based on ever-refining multifunctional cellulose carriers, leading to novel paths for more efficacious treatment [104].

7 Conclusion

Cellulose-based drug delivery systems offer a versatile and effective platform for stabilizing and controlling the release of protein and peptide therapeutics. They can be adjusted to fit different drug delivery routes, such as oral, injectable, transdermal, and

mucosal, due to their biocompatibility, biodegradability, and adjustable characteristics. These systems improve medication stability, bioavailability, and targeted release using various cellulose derivatives and sophisticated formulations. Meeting regulatory standards, optimizing large-scale production and guaranteeing protein stability over the long term are all obstacles. Future research should focus on developing smart cellulose-based materials, integrating 3D printing, and exploring combination therapies to further advance precision medicine and clinical applications.

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Chapter 6

Application of Biopolymers in Parenteral Drug Delivery

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Abstract The incorporation of biopolymers (BIPs) in the development of therapeutic delivery systems is gaining popularity due to its multiple advantages over traditional polymers. BIPs offer numerous advantages, including biodegradability, biological compatibility, sustainability, cost-effectiveness, and availability, making them ideal for producing materials for biomedical applications. Additionally, BIPs are appropriate as they enrich functioning and boost human life. In pharmaceutical treatments for acute and critical disorders, parenteral medication delivery is essential. As lyophilization aids, medicinal components, and drug carriers, polymers are essential formulation ingredients. In addition to offering therapeutic benefits and shelf-stability, they also alter the pharmacokinetic and pharmacodynamics behavior of drugs in vivo, increasing therapeutic activity, decreasing toxicity, and focusing on specific organs or cells. BIPs are generally utilized as a carriers in various drug delivery system like nanoparticles, hydrogels or micellar formulation which may enhance the bioavailability of the drug. They can be also used for targeted drug delivery system. This chapter emphasizes the types of BIP used for parenteral formulation and their mechanism of action with their application regulatory consideration.

Keywords BIPs · Parenteral drug delivery · Application

1 Introduction

As a substitute for synthetic polymers in applications involving controlled release and encapsulation, BIPs have seen exponential growth in research in the twenty-first century. They present a viable substitute for chemical substances and organic

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solvents and can ensnare drugs that are simultaneously hydrophilic as well as lipophilic. Protein-polysaccharide blends and coacervation techniques can produce novel matrices for controlled-release uses [1]. BIPs are biodegradable substances with a carbon, oxygen, and nitrogen backbone that are made from natural or plant-based resources like crops and horticulture. They offer benefits such as renewability, biocompatibility, cost, and carbon release, and they are easily recycled through biological processes. Additionally, BIPs are easily ecologically benign, safe, non-carcinogenic, and non-thrombogenic [2]. Parenteral drug delivery uses injections or infusions to administer pharmaceutical substances without going through the digestive system. Benefits of BIPs derived from natural sources include functionalization for particular drug delivery applications, biocompatibility, and biodegradability. Because they provide regulated release, targeted distribution, and fewer adverse effects, they are attractive for complicated medicinal compounds. Concerns of stability, immunogenicity, regulatory barriers, and large-scale production never go away. This section examines the principles of BIPs, their use in parenteral drug delivery, and their difficulties, in addition to evaluating new findings and potential future therapeutic applications. The many types of BIPs, their issues, uses, and regulatory ramifications for parenteral drug delivery are covered in the current chapter.

2 Fundamentals of BIPs

2.1 *Types of BIPs Used in Parenteral Drug Delivery*

There are four types of biodegradable polymers: agro-BIPs, microorganisms, biotechnology, and petrochemical compounds. The most extensively investigated are biomass products, which include plant and animal proteins, lipids, and carbohydrates. Natural sources of BIPs include microorganisms found in plants, animals, algae, and agricultural waste. These materials include flexibility, softness, and a gel-like consistency, combining the qualities of both solids and fluids [3–11].

BIPs made from proteins and polysaccharides are more desirable than synthetic ones because of their favorable antibacterial, low immunogenicity, biodegradability, and biocompatibility characteristics. Selecting the right biomaterial for medication administration is crucial because of the potential for toxicity from degradation. The biodegradation of polysaccharides by enzymes, for example, results in byproducts that need to be carefully studied before being employed in drug delivery systems [12].

2.1.1 Polysaccharides

Higher molecular mass derivatives of monosaccharides having units that recur polysaccharides have polymeric character. In DDSs, starch, cellulose, alginate, and Chits are among the more often used surface-modified carbohydrates (Fig. 6.1). [13].

Chitosan (Chits)

It is a common, safe BIP that has been extensively investigated for an assortment of therapeutic applications [14–16]. It transforms the naturally occurring polymer chitin into a cationic polysaccharide composed of D-glucosamine and *N*-acetyl. The exoskeletons of insects, mollusks, annelids, fungus, and crustaceans naturally contain it [17]. It is also mucoadhesive, hemostatic, biocompatible, and adhesive [15, 16, 18]. It serves as a BIP that is used in DDSs in a variety of variations, including gels, films, beads, oral tablets, and microspheres for oral, nasal, ocular, and transdermal routes. The material is odorless, recyclable, biocompatible, and safe, and it has antimicrobial effects [19, 20]. Additionally, Chits' anti-tumor and anti-fungal qualities are crucial for the creation of bio-dental content, the management of periodontitis, and the regeneration of tooth pulp [21]. Chits can be injected, parenteral, nasally or vaginally. Controlling drug dispersion from the substance to the desired doses while achieving drug absorption and stability is a significant advantage of using Chits in DDSs [20].

Incorporating Chits via a variety of synthetic and natural polymers, such as polylactic acid, sodium alginate, polycaprolactone, poly(vinyl pyrrolidine), poly(ethylene oxide), and graphene oxide, can alter the qualities of the substance [22, 23]. Chitosan can interact with other polymers and biological materials thanks to its $-NH_2$ and $-OH$

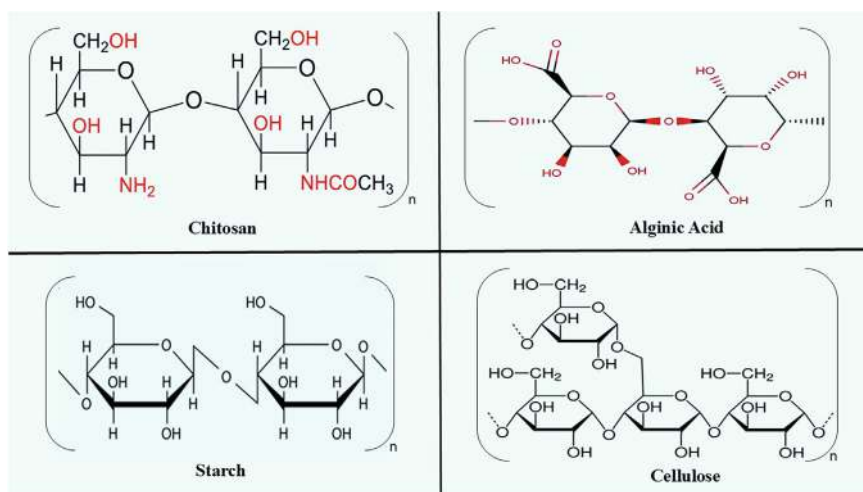


Fig. 6.1 Most prominent polysaccharide chemical structure for creating DDSs

groups. As a result, chitosan can be used alone or in conjunction with other materials to create a variety of innovative nanocarriers, including films, foams, beads, hydrogels, nanoparticles, gels, nanofibers, and sponges [24, 25]. Such combinations strengthen both the mechanical and physiological characteristics of the drugs as well as their release mechanism [26].

Chen and associates grafted, cross-linked, and compounded dopamine and sodium dialdehyde alginate to generate a Chits hydrogel for the therapy of prostate cancer along with the administration of medications. The drug-delivery hydrogel that was developed revealed remarkable organ-wall adherence along with targeting capabilities. Additionally, the hydrogel's 99% biocompatibility and 98% antimicrobial qualities were demonstrated [5]. For the management of carcinoma of the breast, a combination nanoparticle of carboxymethyl Chits customized via calcium phosphate along with folate then loaded using curcumin has been produced. The final products showed adequate biological suitability, stability, and pH-responsive medication release. The results showed that products founded on carboxymethyl Chits had an organelle-specific targeting treatment approach for cancer [27].

In one study, the molecular weight of Chits had a substantial impact on the characteristics of polyplex nanoparticles used for gene transfer. Chits-based nonviral vectors are more stable and suited for gene therapy due to their lower molecular mass along with nitrogen/phosphorus ratio [28]. The degree of deacetylation to generate poly-D-glucosamine is a crucial factor in the formation of nanoparticles for gene therapy [29]. As a result, D-glucosamine's amine groups allow it to conjugate with certain cross-linkers, forming covalent interactions with molecules and enabling targeted gene therapy to specific categories of cells. To sum up, these crucial qualities make Chits an appropriate polymer for creating novel nonviral vectors [30].

Because of their better functional properties in DDSs and their capacity to target precise, non-invasive tissue regions, injectable hydrogels have recently attracted attention. Therefore, developing DDSs that respond to hydrogel stimuli, have several benefits, and release a medication in response to an external stimulus is a difficult task. Thus, chits-based hydrogels are particularly promising for tissue construction and medication administration because of their biocompatibility, mucosal adhesiveness, along with hemostatic behavior [31].

Alginate

It is also a commonly used BIP that is employed in the healthcare industries owing to their exceptional enveloping attributes and function in bruise repair. It has been used extensively since its initial isolation in the 1980s due to its various advantages, which include being a mucoadhesive, biocompatible, renewable, biodegradable, and readily available material. Additionally, it is immunogenic and non-toxic. This BIP is utilized as an excipient in the pharmaceutical sector for the management of reflux esophagus inflammation [32, 33]. Brown algae produce alginate, which is the calcium, magnesium, sodium and magnesium salts of a substance called alginic

Table 6.1 Starch analogues for parenteral therapy

Drug	Variety	References
Tobramycin; Colistin	Oxidized	[48]
Ibuprofen	Acetylated	[49]
Doxorubicin	Hydroxyethyl	[50]

acid. A multitude species of bacterial, including *Azotobacter vinelandii* along with various *Pseudomonas* species, have the potential of completing this synthesis [34].

Alginate extraction entails grinding algae, washing with acid, and heating alkali. It is then acidified and treated with oxides to produce metallic gels containing various cations. These gels remain stable between 0 and 100 °C, but may dissociate when exposed to acids. Alginate is commonly combined with BIPs to avoid breakdown in digestive fluids [35]. Dual cross-linked Chits/alginate hydrogels were created by Hoang et al. for pH-responsive medication administration. When tested, the hydrogels showed minimal cytotoxicity to human cells and a lipophilic drug loading capacity of less than 50% w/w indicating their biocompatibility [36]. Li and associates developed a pectin/Chits BIP hydrogel that responds to temperature and pH for application in drug delivery systems. The resulting hydrogels were demonstrated to be biocompatible and to have a high capacity for self-healing, with no negative effects on mouse fibroblast cells [37].

Starch

Starches, synthetic as well as natural, have proven frequently employed as recyclable, sustainable, biocompatible, and harmless polysaccharides in a number of therapeutic utilization, including administering medication as well as the development of tissues [38–43]. It is generally employed as a transporter and, in some applications like bone transplants along with regeneration, can be separated from natural sources such as corn, rice, wheat, and potatoes [13]. In addition to these benefits, native starch has certain drawbacks, including poor aqueous solubility, the production of semisolid formulations like gels with irregular textures and viscosities, degradation at various high temperature and pH settings, and freeze–thaw fluctuations [44, 45]. To improve the physicochemical or biological features of a substance for the manufacture of DDSs, many modifications (physicochemical as well as enzymatic) are required [46].

In one of the research, a unique nanoparticulate system was crated for acetylated starch nanocrystals utilizing broken rice, implying that they could be effective for controlling doxorubicin administration in cancer treatment [47]. Table 6.1 presents further examples of starch analogues which have proven useful for delivering medications.

Thomas and colleagues used an eco-friendly technique to create starch-modified alginate nanoparticles for medication delivery. Theophylline and bovine serum albumin were employed as model medicines to assess their potential in controlled

medication delivery applications. The *in vitro* drug release tests revealed pH-dependent features, and the produced nanoparticles exhibited good encapsulation efficiency. Additionally, the produced nanoparticles were demonstrated to be biocompatible with L929 fibroblast cell lines. Consequently, it was shown that the created materials were a potential instrument for the application of drug delivery [51].

Cellulose

Cellulose, the most widely used BIP, is strong, renewable, and biodegradable. Its backbone is full of hydroxyl groups, and it is made up of glucose units. Cellulose has several drawbacks, including limited use due to its extremely low solubility in water and typical organic solvents [52–54]. Because it is environmentally friendly, simple, and presents low cost and toxicity, an aqueous sodium hydroxide (NaOH)/urea solution is frequently used to dissolve cellulose [55, 56]. A versatile and suitable material for DDSs is cellulose derived from a variety of sources [57, 58]. To administer the medication silver sulfadiazine, AL-Rajabi and Teow created a sustainable manufacturing process for a thermoresponsive Pluronic F127 composite hydrogel reinforced with cellulose extracted from empty oil palm fruit clusters. Their research showed that the material made from abundant agricultural biomass is economical, environmentally benign, and sustainable for use as DDSs [59].

Hyaluronan

N-acetyl-D-glucosamine and D-glucuronic acid disaccharide repeats are found in hyaluronan, a linear polymer. Despite being a straightforward linear chain, it possesses a number of significant biomechanical characteristics [60]. It has been shown that hyaluronan has high viscoelasticity, biocompatibility, and biodegradability. It can also be combined with particular cell surface receptors [61]. Because it can identify particular receptors that are overexpressed on the surface of tumor cells, hyaluronan has gained interest as a drug delivery vehicle. This allows cancer medications to be tailored to the tumor cells to more effectively eliminate them. Hyaluronan has been widely utilized in targeted and controlled-release DDSs. Up until now, the majority of research has only been conducted *in vitro*; *in vivo* tests are used in very few studies. However, it is thought that when new materials and technologies are developed, the potential of hyaluronan as a drug carrier will increase. Many studies on hyaluronan as a drug carrier are presented in the literature, however the majority are still in the laboratory study stage. It is challenging to industrialize hyaluronan due to the intricate processes involved [62].

Dextran/Cyclodextrins

Due to its availability, hydrophilicity, biocompatibility, non-toxicity, non-immunogenicity, and biodegradability, dextran has garnered significant interest among the aforementioned polysaccharides for use as nanoscale drug carriers [63]. Numerous microbes can biosynthesize dextran either intracellularly or extracellularly. Commercial dextran, a significant source of nitrogen, is often produced by fermenting *L. mesenteroides* or *L. dextranicum* in a medium containing sucrose. It is advised that fermentation-derived dextran be minimally altered in order to produce highly biocompatible DDSs. On the other hand, a reduction in biocompatibility or an increase in cytotoxicity is noted if the structure of dextran is altered. This has led to the removal of numerous DDSs from in vivo or clinical studies that contained acetylated, diethyl aminoethyl-dextran, carboxymethyl, or the sodium salt of dextran sulphate.

For use in pharmaceutical and medical applications, many DDSs containing dextran were created as liposomes, hydrogel, micelles, microspheres, micro- and nanoparticles, and medical adhesives [64]. Grafted dextran-based micelle production for DDSs in anticancer therapy has drawn a lot of attention lately [65]. Dextran is coupled with lipids including oleic acid, stearic acid, and cholesterol to create amphiphilic polymers that can form micelles and trap chemotherapeutic drugs. These polymers escape renal extraction, are very stable, and quickly reach the target cell [66].

The enzymatic breakdown of starch yields cyclodextrins, which are biocompatible and biodegradable substances. Cyclodextrins and their derivatives are a significant family of pharmaceutical excipients that have been used in recent decades to improve the therapeutic efficacy of numerous medications. In DDSs, they are the smallest nanocarrier [67]. Using β -cyclodextrin, Pedotti et al. created a release mechanism for the antiviral medication Acyclovir. To assess the prodrug's potential for usage in various administration methods, they assessed its hydrolysis in physiologically simulated environments.

Acyclovir's release was examined in the presence of pig liver esterase and in both acidic and neutral environments. Within seven days, 100% of free acyclovir succinate and acyclovir were released in each case, albeit at varying rates depending on the hydrolysis conditions [68]. Di Cagno et al. assessed the potential of new β -cyclodextrin-dextran polymers for drug delivery. According to the findings, every polymer under investigation had a size that was appropriate for parenteral delivery. Compared to the native polymer and other commercially available derivatives, the stability of the polymer/drug complex was unaffected by the presence of the dextran backbone structure. The drug release studies showed that the diffusion of the hydrocortisone drug was influenced by the Solubilization induced by the developed polymer derivatives [69].

2.1.2 Proteins

Proteins are high molecular weight molecules commonly utilized in DDSs. Silk's fiber, collagen, gelatin, with albumin are frequently employed animal-derived proteins for DDSs [13].

Albumin

With 50% of all plasma proteins being albumin, it is the most abundant protein in plasma and performs a vital physiological role in the human body [70, 71]. To be more precise, albumin is an internal amino acid supply. Additionally, it helps maintain the plasma's steady osmotic pressure. At a pH of 7, albumin is up to 40% soluble in water. Albumin, as a non-specific in nature carrier protein, can form soluble complexes in vivo by combining it with a range of non-soluble chemical molecules and inorganic particles. Albumin's biocompatibility, non-immunogenicity, and biodegradability are some of its beneficial properties [72].

Research into albumin-based protein-based delivery systems for use in ocular applications has increased recently. However, because proteins are constantly vulnerable to enzymatic degradation, unique design strategies are needed to distribute them to specified locations [58, 73]. It's interesting to note that albumin is a highly charged protein that works well for charged bioactive substances' electrostatic adsorption. As a result, albumin-based medication delivery is being thoroughly investigated. Bovine serum albumin has been shown to have therapeutic and medicinal uses among different types of albumin when compared to ovalbumin and human serum albumin [74].

Albumin and hyaluronic acid mixes have been shown to be effective nanocarriers with a number of noteworthy benefits, including effective targeting, drug release that is sensitive to pH and/or hyaluronidase, reducible particle size, the ability to mix several medicines, and excellent durability. Additionally, medications administered by albumin and hyaluronic acid-based nanoparticles have been used to treat skin tissue, joints, malignancies, and the vitreum. Furthermore, there are opportunities for both combined therapy and theranostics with this combination [75].

Silk Fibroin

The proteins that make up silk fibroin are derived from silkworms and spiders. Silk is formed out of a crystalline material called fibroin as well as an amorphous protein termed sericin [76]. Silk, an organic protein, is thought to be a practical organic material for creating DDSs [77]. Biological acceptability, being biodegradable safe degradation products, a range of sterilization options, soft aqueous processing that maintains the medication's bioactive traits, mechanical durability, and self-assembly properties are just a few advantages that silk provides that are pertinent to the creation of sustainable DDSs [78]. Furthermore, several kinds of processing methods are

applied to produce silk delivery system applications, including hydrogels, films, microspheres, lyophilized sponges, silk-coated polymeric particles, nanoparticles, and nanofibers[79].

Studies are creating DDSs that blend silk with other polymers or nanoparticles to lessen the dose of the active pharmaceutical ingredient and its negative influence on healthy tissues. For instance, when encapsulated in silk nanoparticles, the medications Paclitaxel and *cis*-dichloro diamino platinum decreased tumor development and effectiveness. Furthermore, DDSs based on silk are a good substitute because of the silk's sensitivity to pH, as drug release kinetics are consistent at low pH levels [80]. Recently, a copolymer covering of silk fibroin and polymethacrylate was created for oral formulation. Studies carried out both in vitro and in vivo showed that the capsules coated with silk fibroin enhanced pancreatin-dependent medication release. According to other studies, vincristine is delivered to Wilms tumors via a silk fibroin hydrogel, and the drug's release is accelerated by ultrasound. Although the Wilms malignant cells were resistant to increased doses of released medicines, According to the investigation, ultrasound imaging started to raise the degree of cell demise [81].

Collagen and Gelatin

Animals are abundant in collagen, a naturally occurring protein. Because of its biodegradability and biocompatibility, this BIP has been utilized in a variety of formulation, primarily in oral formulation [83]. Collagen also exhibits synergism with bioactive substances and is non-toxic and non-antigenic. Collagen's functional groups are conveniently adjusted for effective oral medicine administration, and it is a vital part of some malignant microenvironments. Because the collagen component can penetrate the tumor site and deliver anti-cancer medicines, this characteristic is advantageous in cancer therapy. Gelatin is a naturally occurring BIP that is produced by hydrolyzing collagen with acids and alkalis. Gelatin is easy to cross-link with other substances and possesses qualities that make it excellent for the administration of chemotherapy drugs. Animals are abundant in collagen, a naturally occurring protein. Because of its biodegradability and biocompatibility, this BIP has been utilized in a variety of DDS applications, primarily in oral formulation [82], Collagen also exhibits synergism with bioactive substances and is non-toxic and non-antigenic. Functional groups in collagen can be easily altered to provide the right characteristics for oral medication administration. Because the collagen component can penetrate the tumor site and deliver anti-cancer medicines, this characteristic is advantageous in cancer therapy. Gelatin is a naturally occurring BIP that is produced by hydrolyzing collagen with acids and alkalis. Gelatin is easy to cross-link with other substances and possesses qualities that make it excellent for the administration of chemotherapy drugs [83].

When gelatin is altered to improve the effectiveness of medication encapsulation, its bioavailability rises. Additionally, gelatin can be specially altered to load

a particular medication. For the oral administration of hydrophobic chemotherapeutics, gelatin is hence ideal [85]. When gelatin is altered to improve the effectiveness of medication encapsulation, its bioavailability rises. Additionally, gelatin can be specially altered to load a particular medication. For the oral administration of hydrophobic chemotherapeutics, gelatin is hence ideal [84]. Nanometric vesicles consisting of a poly(styrene-*b*-ethylene oxide) block copolymer, adapalene, and silver sulfadiazine were utilized as a skin's dressing, combining progressive drug release to restrict infection progression and extended adapalene release to promote skin healing [85]. The study investigates the release of ionic pharmaceuticals via inhaled gelatin particles, exposing their aerodynamic features, biocompatibility, and dispersion. The swelling patterns demonstrate that they can prolong lung residency time by inhibiting macrophage uptake [86].

2.1.3 Nucleic Acids

Supramolecular BIPs called nucleic acids are found in all living things. The most well-known are DNA and RNA, which are essential to biological functions. While RNA works as an intermediary mediator for regulating gene expression, DNA stores and conveys genetic information to other cell components [87, 88]. Furthermore, they take part in the regulation of specific cell activities and the catalysis of specific biochemical reactions [89]. Numerous biomedical applications can benefit from the use of nucleic acids. Drug delivery cannot employ unmodified nucleic acids. However, the variety of medication delivery strategies with the potential for regulated release has rapidly increased due to the development of nucleic acid aptamers and multivalent nucleic acid nanostructures [90].

3 Other Polymers Employed in DDSs

3.1 *Polyamide/Poly(Amino Acid) Polymers*

Among the polymers discussed above, polyamides or poly(amino acid)s stand out for their notable biocompatibility, gradual decline, and changeable physicochemical properties. Repetitive elements in polyamide are connected by amide bonds. Generally speaking, poly(amino acid)s are a collection of tiny polyamides made up of several amino acids of the same kind joined by amide bonds. Polyamide can be synthesized or found in nature [91]. Proteins like silk and wool are examples of naturally occurring polyamides, whilst various compounds like nylon, sodium poly(aspartate), and aramids are examples of synthetically produced ones [92]. Additionally, polyamides can be divided into copolyamides, which have diverse constituents, and homopolyamides, which have a single type of monomer [93]. These polymers

offer several significant benefits when used in DDSs, including stability, consistent release, and localized target site activity. Other drawbacks include the potential for microbiological infection, excessive hydration, and decreased viscosity during storage [94]. Because synthetic poly(amino acid)s resemble naturally occurring ones in structure, they are also utilized in the construction of DDSs [95]. To achieve selective delivery for a reasonable amount of time, poly(amino acid)s are primarily utilized in the fabrication of chemotherapy. These polymers reduce adverse drug reactions and boost anti-tumor activity in DDSs [96].

Polyaspartamide BIP is currently increasing popularity due to its great biocompatibility, ability to degrade, and low toxicity. Furthermore, its physicochemical properties enable flexibility in functionalizing with other components, such as DNA and pharmaceuticals (doxorubicin or biotin), for a variety of biological applications [97, 98]. Using thermal breakdown techniques, researchers developed super paramagnetic iron oxide nanoparticles for cancer detection and treatment. These nanoparticles, encased in polyaspartamide BIP, inhibited tumor volume growth by threefold when compared to control cells [77]. In one of the investigations, a new polymeric product for cancer treatment was produced, demonstrating delayed cytotoxic effects on tumor cells and improved in vivo anticancer effectiveness in NOD-SCID mice [69].

3.2 Dendritic Polymers

Dendritic polymer structures have promising medicinal qualities and may find application in medicine delivery systems. Furthermore, because to its monodispersity, high symmetry, and superficial polyvalency, the dendritic polymer architecture is better to linear polymers for distribution applications [99]. Depending on the method, a dendrimer can bind a drug through exterior surface groups (charge–charge interactions), branching points (hydrogen bonds), or unoccupied spaces (molecular capture). PAMAM dendrimers (Poly(amidoamine) dendrimers), commercially available with amine, hydroxyl, carboxylate, and pyrrolidinone surfaces, as well as related generations, are the most often used dendrimers for drug delivery systems [100].

There have also been reports of easily accessible hyperbranched polymers with core–shell structures. To create pH-sensitive nanocarriers, acetal or imine linkages were used to bind pH-sensitive shells to commercially available dendritic structures (polyglycerol and poly-(ethylene imine)) [101]. These dendritic structures are block copolymers produced from helical polyglycerol-co-polycaprolactone (PG-co-PCL) that are used to give gemcitabine for the treatment of pancreatic ductal carcinoma [102]. Several chemical linkers that react to external stimuli were employed to produce functional dendritic polymer structures as signals-responsive nanocarriers for the transport of bioactive substances [103].

Narayanan et al. created a fourth-generation polylysine dendritic nanocarrier for providing methotrexate to mammary malignancies excessive expression the

epidermal growth factor receptor. The nanocarrier displayed outstanding effectiveness and diminished tumor size in NOD-SCID mice, showing that dendrimer had a more acceptable impact [72] (Table 6.2).

Table 6.2 Procedures for preparation and a list of medications included in the created BIP-based nanoparticles

Drug	BIP	Chemical manufacturing technique	Physical manufacturing technique	References
Methotrexate	Chits	Ionic gelation	Freeze-drying	[105]
Dacarbazine	Chits	Ionic gelation	Ionic gelation	[104]
Curcumin	Chits	Ionic gelation	Freeze-drying	[106]
Chlorpheniramine maleate	Starch	Ionic gelation	Electrospinning	[107]
Hydroxycamptothecin	Starch	Reduction	Dissolution	[108]
Doxorubicin	Starch	Reduction	Dissolution	[109]
Doxorubicin	Carboxymethyl cellulose	Reduction	Freeze-drying	[110]
Tetracycline	Passion fruit peel cellulose	Hydrolysis	Solvent evaporation	[111]
Felodipine	Cellulose	Hydrolysis	Solvent evaporation	[112]
Irinotecan	Albumin	Desolvation	Solvent evaporation	[113]
Curcumin	Bovin serum albumin	Desolvation and chemical co-precipitation	Solvent evaporation	[114]
Diazepam	Albumin	Desolvation and chemical co-precipitation	Solvent evaporation	[115]
5-fluorouracil	Silk fibroin	Crosslinking	Extrusion	[87]
Mouse articular chondrocytes	Methacrylated silk fibroin	Photocrosslinking	Extrusion	[116]
Ibuprofen	Silk fibroin	Photocrosslinking	Supercritical CO ₂	[117]
Doxorubicin	Collagen	Ionic gelation	Electrospinning	[118]
Ciprofloxacin	Collagen	Ionic gelation	Electrospinning	[119]
Cardamom extract	Collagen	Desolvation	Electrospinning	[75]
5-fluorouracil	Gelatin	Crosslinking by desolvation	Supercritical CO ₂	[120]
Econazole nitrate	Gelatin	Crosslinking by desolvation	Supercritical CO ₂	[121]

3.3 BIP-Based Drug Delivery Systems

3.4 Mechanisms of Drug Release in BIP Systems

These days, a lot of research is being done on novel medication delivery methods because of the growing expectations on their quality [122]. One of the reasons DDSs are used is because medicines may be delivered in their most active state or, conversely, can be stabilized by the functionalization of their transporter favored. Furthermore, a DDS guarantees administration into bodily cavities, which would not be feasible in any other way. As a result, these characteristics make these systems more affordable, more effective, and more therapeutic. Various methods can be used to provide drugs based on the patient's needs [123]. Pills, capsules, and injections are utilized to provide a rapid release. Despite their significant clinical uses, their poor pharmacokinetic profile precludes their usage in several therapeutic settings [124]. Implantable devices are used to achieve a prolonged release, which can extend the drug's release across longer duration from days to years. The two most popular uses are in contraception and cures for cancer. However, because the majority of the placed devices are composed of non-biodegradable polymers, they must be surgically removed once the therapy is over [125, 126].

Salamanca et al. discovered that a drug's dissolving rate is determined by the BIP's properties, such as molecular weight and chemical structure. They investigated the release characteristics of gums like Tragacanth and xanthan, which are BIPs with distinct features. Tragacanth gum, which has polarity and limited aqueous solubility, released the drug instantly, but xanthan gum, which contains anions in its chains, released the drug slowly and steadily. The discharge was pH dependent [127].

Diffusion is another technique that is commonly used in the release of therapeutic substances. This phenomenon is defined as the mass transfer of molecules from one part of the system to another through random molecular motions, similar to a concentration gradient.

Polymers can release drugs effectively through diffusion, dissolution, and swelling. Swelling alters material characteristics, affecting medication release and water uptake in hydrogels. Water intake and swelling are driven by dissolving forces that are osmotic, electrostatic, and entropy-favored. There have been various publications published on the swelling behavior of BIPs and hybrid-enhanced BIPs. Osmosis is the process by which solvent passes through a membrane to equalize solute concentration. Osmotic systems are more difficult and inefficient than other drug delivery technologies because the drug core is surrounded by a membrane that allows water to permeate and create osmotic pressure. They provide higher percentages of medicine loading at zero-order delivery rates and better zero-order delivery. Osmotic systems are often composed of cellulose and its derivatives due to its regulated permeability. Erosion and degradation produced by chemical reactions or external stimulation can slow distribution velocity, making these systems suitable for implanted or injectable medicines [119].

3.5 Advantages of BIPs in Parenteral Drug Delivery

As a biodegradable, BIPs decompose into biomass, carbon dioxide, and water. They come from renewable resources. Compared to conventional plastics, they emit fewer hazardous chemicals and are non-toxic. They don't hurt the patient when employed in medical therapy. They break down into organic matter and reduce carbon dioxide emissions [128].

4 Challenges and Limitations

4.1 Stability and Storage Issues

BIPs exhibit high surface tension and a low melting point. BIPs are capable of having complicated structures. Synthesis of BIPs can be costly. Infrastructure for handling BIPs might be lacking. Land use problems may arise from BIPs. If biodegradable polymers are not completely compostable and biodegradable, they may leak metals and methane, among other harmful chemicals [129].

4.2 Immunogenicity and Allergic Reactions

Immunogenicity is the ability of BIPs, even those deemed biocompatible, to trigger an immunological response in the body. When the body's immune system misinterprets a BIP as a dangerous material, certain people may experience allergic reactions. Anaphylaxis, a potentially fatal allergic reaction, can result from severe allergic reactions. The development of antibodies against the BIP due to immunogenicity may counteract its therapeutic impact or change its pharmacokinetic profile. Immunogenicity may also cause glomerulonephritis or vasculitis, among other negative side effects [130].

4.2.1 Factors Influencing Immunogenicity:

Different BIPs have variable immunogenic potential. The manufacturing method can influence the immunogenicity of a BIP. A person's reaction to BIPs may be influenced by their genetic makeup and underlying medical issues. Humanized or chimeric antibodies can still cause anaphylaxis, but their immunogenicity is lower than that of mouse antibodies. By changing the structure of food proteins, BIPs can lessen their allergenicity [131].

5 Applications of BIP-Based Parenteral Drug Delivery

5.1 Protein and Peptide Drug Delivery

Parenteral drug delivery systems based on BIPs are a novel method of effective protein and peptide drug administration that offers solutions to problems like poor oral bioavailability and patient discomfort due to frequent injections. Naturally occurring BIPs like Chits, alginate, and gelatin are used because they are biodegradable and biocompatible, minimizing the chances of inducing an immunogenic response. BIPs stabilize the drug, retain the active ingredient against degradation, and provide a controlled release profile, enabling the drug to have the potential to prolong therapeutic effects. BIPs have good encapsulation properties, increasing drug loading capacity with integrity. Additionally, BIPs are easily chemically modified for changing their properties according to desired application, offering themselves as very good platforms for enhancing parenteral therapies in terms of efficacy and safety. Overall, BIP-based systems are an important step in maximizing the delivery of protein and peptide drugs, leading to improved patient outcome and compliance [132, 133].

Polymeric nanoparticles (NPs) augment protein and peptide uptake through parenteral, nasal, and transdermal delivery through facilitated cellular uptake and penetration through biological barriers. They facilitate sustained drug release in parenteral delivery and increase the systemic uptake in nasal delivery, avoiding first-pass metabolism. In transdermal delivery, the permeability is facilitated through skin modification or microneedles. Polymeric NPs in general increase the bioavailability and therapeutic activity of protein and peptide drugs very substantially [134].

Additionally, polyester-based carriers, particularly poly(lactic-co-glycolic acid) (PLGA), are widely used for their excellent controlled release properties and have been integrated into FDA-approved formulations. PLGA's biodegradability and ability to customize drug release profiles make it an effective choice for long-acting drug delivery systems. These characteristics allow for sustained therapeutic effects, reduced administration frequency, and enhanced patient compliance, demonstrating PLGA's significance in advancing modern drug delivery technologies [135].

Overall, the use of BIPs in drug delivery systems significantly enhances therapeutic efficacy while providing new avenues for increased patient compliance and effectiveness. With their biodegradability, biocompatibility with capability to provide controlled release, BIPs enhance the delivery of many therapeutics, eliminating problems with low bioavailability and multiple dosing. The approach not only allows for more effective treatment regimens but also promotes greater patient compliance and satisfaction [134, 135].

5.2 Vaccine and Gene Development

BIP-based systems are also being developed as a multi-directional platform for parenteral drug delivery, vaccines, and gene therapy, leveraging their inherent properties of biodegradability, biocompatibility, and non-toxicity. These properties position BIPs as the best option to ensure safe and efficient delivery of therapeutic products. Various BIPs like Chits, alginate, and silk fibroin have been extensively explored for drug as well as genetic material encapsulation, stabilizing them to a large extent and offering a controlled release pattern [136].

This encapsulation has the added effect of shielding sensitive biomolecules from degradation and thus enhancing their bioavailability. The versatility of BIP-based systems allows customized formulations to be developed to treat individualized medical conditions, and they are therefore well-suited to the formulation of therapeutic strategies in contemporary medicine. With ongoing research, opportunities for BIP-based systems will increase, enabling improved patient outcomes and compliance through enhanced treatment efficacy [2, 135, 137].

Chits has also proved to be a very promising non-viral vector for gene delivery because of its structural stability, biocompatibility, and the simplicity of chemical modification. Its cationic nature facilitates effective encapsulation of anionic nucleic acids, and chemical modification allows the introduction of solubility and targeting capabilities. Its biodegradability also offers low toxicity and allows for controlled release of genetic material. All these characteristics render Chits as a multi-functional vehicle for gene therapy application development [137].

Polymeric nanoparticles have demonstrated great potential in vaccine delivery through the provision of immunomodulatory activity and shielded protection of antigens from degradation. Their nanometric dimensions improve stability and enable targeted delivery to antigen-presenting cells, enhancing immune responses. They can also be designed to enable controlled release and co-delivery of adjuvants, making them useful tools in the design of more effective and persistent vaccine formulations [138].

Recent advancements in the production of BIP-based formulation exhibit their potential in targeted therapy for a range of medical uses, including cancer treatment and tissue engineering. Development of material design and processing techniques has enabled the production of highly selective delivery vehicles capable of targeting specific cells or tissues, thereby enhancing therapeutic efficacy with fewer side effects. In addition, the inherent biocompatibility and biodegradability of BIPs make them ideal candidates for the delivery of therapeutic agents in a controlled fashion. These advancements not only optimize the results of treatment but also pave the way for the establishment of customized medicine strategies tailored to individual patient needs [132, 139].

In general, incorporation of BIPs into drug delivery systems is a significant step towards increased therapeutic effectiveness and patient benefit.

5.3 Anticancer Drug Delivery

BIP-based parenteral drug delivery systems have been recognized as promising anticancer therapy platforms that effectively address key challenges related to traditional treatments, such as non-specificity and systemic toxicity. Using biodegradable polymers, these systems enhance targeted delivery of drug loads to tumor tissues, extending therapeutic efficacy. Targeted delivery minimizes harmful impacts on healthy cells, reducing side effects traditionally linked to conventional chemotherapy. In addition, the potential for designing these BIP systems for controlled release further enhances drug delivery, leading to more effective and less toxic cancer treatment regimens [140, 141].

Significantly, stimuli-responsive BIPic systems can release drugs intelligently under specific conditions in the tumor microenvironment, e.g., pH or temperature. Targeted release ensures action at a specific site, where the drug is released precisely where it is needed most, thereby enhancing therapeutic efficacy with reduced systemic side effects. Because of the potential to respond to the unique characteristics of the tumor environment, such systems can enable sustained release of the therapeutic agent, improve treatment efficacy, and facilitate more effective anticancer therapies. Such advances further highlight the potential of BIPic drug delivery systems to provide personalized and responsive cancer therapies [142].

Various BIPs, i.e., proteins and polysaccharides, have been thoroughly studied for their better properties that guarantee effective encapsulation of drugs and protection from degradation. Proteins, i.e., gelatin and albumin, provide biocompatibility and can generate hydrogels that improve drug stability and release profiles. Polysaccharides, i.e., Chits and alginate, have good properties, i.e., biodegradability and nanoparticle formation, that improve encapsulation of a wide range of therapeutic agents. These BIPs not only improve drug stability and solubility but also guarantee controlled release, which is of utmost significance in achieving maximum therapeutic benefits and preventing side effects [136, 143].

Aerogels made from BIP are efficient smart platforms for drug-controlled release that increase the precision of anticancer treatment. High medication loading capacity and adjustable drug release are made possible by their porous nature. They maximize therapy effectiveness and minimize adverse effects by reacting to certain stimuli, which opens up new avenues for cancer treatment [141]. Overall, these advances demonstrate the effectiveness and utility of BIP-based systems in transforming cancer treatment modalities. By facilitating targeted drug delivery, controlled release, and intelligent response to the tumor microenvironment, BIP-based platforms dramatically improve therapeutic efficacy with fewer side effects. Their capacity to encapsulate a wide range of therapeutic agents, coupled with biodegradability and biocompatibility, makes BIP systems revolutionary tools in cancer warfare. As advances in research continue to unfold, these new strategies are likely to enhance patient-specific therapies and cancer care in general [136, 144].

5.4 *Hormone and Enzyme Replacement Therapy*

BIP-based parenteral drug delivery systems have appeared to play central roles in hormonal and enzyme replacement therapies by taking advantage of their biocompatibility, biodegradability, and low immunogenicity to optimize therapeutic efficacy. By using natural polymers like Chits, alginate, and collagen, these systems can be designed to control drug release profiles, leading to enhanced pharmacokinetics and reduced toxicity. Such customization offers sustained and controlled release of therapeutic agents, leading to optimal delivery of hormones and enzymes over time, which optimizes the success of the treatment. Overall, such innovation in BIP-based systems is of great promise to optimize the efficacy and safety of replacement therapies [145, 146].

The biocompatibility and biodegradability of BIPs enable the formulation of formulations that provide sustained release of enzymes or hormones, which is crucial in the therapy of diseases requiring accurate dosing and timing. By designing BIP structures in a controlled fashion, researchers can achieve customized release profiles that are appropriate for the specific requirements of patients. The BIP-controlled release mechanism provides a sustained therapeutic effect, reducing the frequency of dosing and enhancing patient compliance. Additionally, the biocompatibility and biodegradability of the formulations minimize the risk of side effects, further justifying their applications in hormonal and enzyme replacement therapy. Overall, BIP-based systems can significantly improve the efficiency of treatments that require high accuracy in drug delivery [146] [147].

Advances in BIP gel technology have moved towards the development of intelligent drug delivery systems that can detect changes in physiology. Such intelligent systems can be activated by pH, temperature, or biomolecule presence, enabling controlled drug release. Such sensitivity optimizes therapeutic action by providing drugs at the right time and dosage individualized to patient requirements. BIP gels thus hold the promise of being an exciting direction towards optimizing therapeutic efficacy in a broad range of therapeutic applications. Their versatility and adaptability hold enormous potential in patient-specific care [148]. Overall, the use of BIPs in parenteral delivery systems enhances treatment stability and efficacy and offers potential for targeted therapy in critical medical applications. Through the exploitation of the intrinsic properties of BIPs, such as biocompatibility and modifiable release profiles, these systems can maximize drug bioavailability and minimize side effects. Such innovation enables more targeted therapy delivery, particularly in multifactorial diseases like cancer, hormonal imbalances, and enzyme deficiencies. As development proceeds, BIP-based delivery systems will have a vital role in designing new and effective treatment regimens that address diverse medical requirements. Their potential is even greater, with great promise for enhanced patient care and therapeutic outcomes [132, 136].

The application of BIP for parenteral drug delivery is highlighted in Table 6.3.

Table 6.3 Application of BIPs for parenteral drug delivery

BIP	Properties	Applications	References
Chits	– Biocompatible, biodegradable, mucoadhesive – pH-responsive	– Sustained release of drugs – Targeted cancer therapy	[149]
Alginate	– Biocompatible, gel-forming, mild gelation conditions	– Encapsulation of proteins and peptides – Injectable hydrogels	[150]
Poly (lactic-co-glycolic acid) (PLGA)	– Biodegradable, tunable degradation rates – FDA-approved	– Long-acting injectables – Controlled release of small molecules	[151]
Hyaluronic acid	– Biocompatible, non-immunogenic, viscoelastic	– Sustained drug delivery – Ocular and intra-articular injections	[152]
Gelatin	– Biocompatible, thermoresponsive, cost-effective	– Injectable hydrogels for protein delivery – Tissue engineering	[153]

6 Recent Advances and Innovations

6.1 Nanoformulations and Targeted Drug Delivery

Drug delivery has been transformed by nanotechnology through the use of BIPs in tailored systems and nanoformulations. By permitting precise targeting to particular tissues, cells, or organelles, these materials improve drug stability, solubility, and bioavailability, hence increasing therapeutic outcomes. Various types of BIP formulation are highlighted in Fig. 6.2

6.1.1 BIPic Nanoparticles

Hydrophobic medications, proteins, and nucleic acids are frequently encapsulated in BIPic nanoparticles, which are generally 10–1000 nm in size. Because of their biocompatibility and capacity to alter surface characteristics for targeted administration, natural polymers such Chits, alginate, gelatin, and hyaluronic acid are frequently used. Chits-based nanoparticles are perfect for delivering anticancer medications, vaccinations, and gene treatments because of their mucoadhesive qualities and capacity to improve cellular absorption, which have been well investigated [154]. Alginate nanoparticles are known for their pH-responsive behavior, which allows for controlled drug release in acidic environments such as tumor tissues [151]. Hybrid nanoparticles, such as PLGA nanoparticles coated with Chits, have shown improved stability and targeted delivery to cancer cells [155].



Fig. 6.2 Different applications of biopolymers

Recent innovations include the surface modification of BIPic nanoparticles with ligands such as folic acid, antibodies, or peptides to enable active targeting of specific receptors overexpressed in diseased tissues, such as cancer cells or inflamed endothelial cells.

6.1.2 Micelles and Self-assembled Systems

Polysaccharide-based micelles, such as those made from dextran or pullulan, have been utilized to deliver chemotherapeutic agents with enhanced tumor accumulation. Amphiphilic block copolymers self-assemble to generate BIP micelles, which are another intriguing vehicle for targeted drug delivery. By encasing hydrophobic medications in their core and presenting a hydrophilic exterior, these micelles can increase bloodstream solubility and circulation time [156]. A triggered micelles, which release their payload in response to pH, temperature, or redox changes, have been developed for targeted cancer therapy [157]. For example, albumin-based micelles have been utilized for the delivery of paclitaxel, demonstrating enhanced tumor targeting and reduced systemic toxicity [158].

6.1.3 Hydrogels for Sustained and Localized Delivery

BIPic hydrogels, three-dimensional networks of crosslinked polymers, are widely used for prolonged and localized drug delivery. These hydrogels can be injected inside body, where they form a depot that gradually releases the encapsulated drug over time. Hyaluronic acid-based hydrogels have been employed for the delivery of growth factors and stem cells in regenerative medicine, as well as for the localized delivery of chemotherapeutic agents in cancer therapy [159]. Parental in situ-forming hydrogels which exhibit sol-to-gel transitions with consequence of physiological cues such as temperature or pH have the benefit of minimally invasive administration and exact localization of the medication at the target region. Injectable in situ-forming hydrogels that undergo sol-to-gel transitions in response to physiological cues such as temperature or pH have the benefit of minimally invasive administration and exact localization of the medication at the target region [160].

6.1.4 Targeted Drug Delivery Systems

Tailored therapeutic delivery systems utilize BIPs' unique features to route medicinal medicines to specific tissues or cells, increasing efficacy while lowering negative effects. Active targeting entails binding targeting ligands, like antibodies, peptides, or aptamers, on the exterior of BIPic carriers. For instance, transferrin-conjugated nanoparticles have been created for targeting malignant cells which overexpress transferrin receptors [161]. The strategy of passive targeting is based on the enhanced permeability and retention (EPR) impact, which allows nanoparticles to collect preferentially in tumor tissues owing to leaking arteries and veins as well as insufficient lymphatic outflow [14, 162].

6.2 BIP-Based Implants

BIP-based implants provide targeted and sustained pharmaceutical release throughout a lengthy period of duration, minimizing the demand for repeated administration along with raising compliance among patients. Natural polymers like collagen, Chits, alginate, and poly(lactic-co-glycolic acid) (PLGA) are commonly used in the production of implants. Implants made of Chits have been utilized to discharge hormones, anticancer medications, and antibiotics under regulated conditions. They are perfect for mucosal applications because of their mucoadhesive qualities [149]. PLGA-based implants are frequently employed for long-term medication administration due to their customizable breakdown rates and the ability to encapsulate both hydrophilic and hydrophobic medicines [163]. Collagen-based implants are used in regenerative medicine and wound healing, where they provide a scaffold for tissue regeneration while delivering growth factors or antibiotics [164]. Recent

innovations include 3D-printed implants made from BIPs, which allow for personalized drug delivery and complex geometries tailored to specific anatomical sites [165].

6.3 BIP-Based Microneedles

Drugs are delivered straight into the dermis or bloodstream using microneedles, which are minimally invasive instruments that pierce the epidermis. Because BIPs are biocompatible and can dissolve or disintegrate after drug delivery, they are perfect for creating microneedles. Insulin, vaccines, and other biologics are delivered transdermally using soluble microneedles derived from pullulan or hyaluronic acid. When inserted, these microneedles disintegrate, releasing the medication that is contained [166]. Hydrogel-forming Microneedles made from polyvinyl alcohol (PVA) or carboxymethyl cellulose (CMC) swell upon contact with skin interstitial fluid, releasing the drug in a controlled manner [167]. Coated Microneedles use BIPs like Chits or alginate as coatings to deliver drugs directly into the skin without the need for needle insertion [168]. Microneedles are particularly useful for pain-free vaccination, diabetes management, and cosmetic applications.

6.4 Personalized Medicine and BIP Applications

Personalized medicine is revolutionizing healthcare by personalizing therapies to specific patient features such as genetics, disease profile, and lifestyle. BIPs play an important role in enabling personalized treatment because of their biocompatibility, biodegradability, and ability to distribute medications in a regulated and targeted manner.

6.4.1 Role of BIPs in Personalized Parenteral Drug Delivery

BIPs are ideal for personalized medicine in parenteral drug delivery because they can be engineered to meet specific patient needs. Their features, such as degradation rate, mechanical strength, and drug release kinetics, can be adjusted to meet unique therapeutic needs. BIPs like PLGA, Chits, and hyaluronic acid can be modified to achieve specific drug release profiles, ensuring optimal therapeutic outcomes for individual patients [165]. Hydrogel formation when polyvinyl alcohol (PVA) or carboxymethyl cellulose (CMC) Microneedles come into contact with skin interstitial fluid, they expand and release the medication in a regulated way. [149]. Advanced fabrication techniques, such as 3D printing, allow for the creation of patient-specific drug delivery systems with complex geometries [169].

6.4.2 Applications of BIPs in Personalized Parenteral Drug Delivery

3D-Printed Implants for Parenteral Delivery

3D printing technology has altered personalized medicine by enabling the creation of customized implants for parenteral drug administration. PVA or PLGA 3D-printed implants can be programmed to dispense medications at specific times based on the patient's requirements. The age, weight, and severity of the patient's ailment can all be considered when personalizing implants. By administering drugs directly to the intended site, implants reduce the systemic side effects [165].

Injectable Hydrogels for Sustained Drug Release

Injectable hydrogels made from BIPs are used for sustained and localized drug delivery in personalized medicine. Hyaluronic acid-based hydrogels can be injected into the body, where they form a depot that gradually releases drugs over time. Hydrogels can be administered via injection, reducing the need for surgical implantation. The degradation rate and drug release kinetics can be tailored to the patient's needs [159].

Microneedles for Personalized Transdermal Delivery

Microneedles made from BIPs are used for pain-free and minimally invasive drug delivery, particularly for vaccines and chronic disease management. Dissolvable microneedles made from hyaluronic acid **or** pullulan can be customized to deliver precise doses of insulin or vaccines based on the patient's needs. Patients can self-administer microneedles without the need for healthcare professionals. Customizable Formulations: Microneedles can be designed to deliver multiple drugs or vaccines in a single patch [166].

7 Regulatory and Clinical Considerations

The development and commercialization of BIP-based parenteral drug delivery systems require careful attention to regulatory guidelines and clinical considerations. While BIPs offer numerous advantages, such as biocompatibility and biodegradability, their translation from the lab to the clinic involves addressing challenges related to safety, efficacy, large scale applicability and regulatory compliance. This section discusses the key regulatory and clinical considerations for BIP-based parenteral drug delivery systems.

7.1 *Regulatory Pathways for BIP-Based Drug Delivery Systems*

To guarantee their safety and effectiveness, BIP-based medication delivery systems need to adhere to strict regulatory standards. Guidelines for the creation and approval of such systems have been created by regulatory bodies including the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA). Biocompatibility Testing: To make sure BIPs don't cause toxicity or unfavorable immunological reactions, they must pass stringent biocompatibility testing. Assessments of immunogenicity, hemocompatibility, and cytotoxicity are among the tests [170]. Good manufacturing practices (GMP) must be followed during the manufacturing process to guarantee the final product's quality, consistency, and purity. To prove their safety and effectiveness, BIP-based systems need to go through preclinical and clinical testing. Phase I (safety), Phase II (effectiveness), and Phase III (large-scale testing) studies are included in this [171].

7.2 *Challenges in Regulatory Approval*

Despite their potential, BIP-based drug delivery systems face several challenges in obtaining regulatory approval. Scaling up production from the lab to industrial levels while maintaining quality and consistency is a major challenge. BIPs are often complex and heterogeneous, making their characterization and standardization difficult. The long-term safety of biodegradable polymers, including their degradation products, must be thoroughly evaluated.

7.3 *Clinical Considerations for BIP-Based Systems*

The successful clinical application of BIP-based drug delivery systems depends on addressing several key considerations. The design of BIP-based systems must account for patient-specific factors, such as age, weight, disease severity, and genetic profile. BIPs must preserve the encapsulated medicine from degradation and ensure its stability during storage and delivery. Systems for delivering parenteral drugs must be made to be administered safely and effectively by subcutaneous, intramuscular, or intravenous means.

7.4 Case Studies of Approved BIP-Based Systems

Numerous medication delivery methods based on BIPs have made it through the regulatory process and are currently being employed in clinical settings. Breast cancer, pancreatic cancer, and non-small cell lung cancer can all be treated with Abraxane[®], an albumin-bound paclitaxel nanoparticle formulation [172]. Lupron Depot[®] is a PLGA-based microsphere formulation that treats endometriosis and prostate cancer by releasing leuprolide acetate in a regulated manner [173]. The FDA (2018) approved Onpattro[®], a lipid nanoparticle-based siRNA delivery technology, to treat hereditary transthyretin-mediated amyloidosis [174].

8 Future Prospects of BIPs in Parenteral Drug Delivery

The future of BIPs in parenteral drug delivery is poised for transformative advancements, driven by emerging technologies, novel materials, and innovative applications. Below are some new and unique prospects that highlight the potential of BIPs in this field.

8.1 Gene Therapy and Nucleic Acid Delivery

BIPs are increasingly being explored for the delivery of nucleic acids (e.g., DNA, RNA) in gene therapy and personalized medicine. Chits and polyethylenimine (PEI) nanoparticles are being used to deliver siRNA and mRNA for the treatment of genetic disorders and cancers [175]. BIPs protect nucleic acids from degradation and enhance their cellular uptake, enabling targeted gene therapy [13].

8.2 Bio-Inspired and Biomimetic Systems

Future BIP-based systems will draw inspiration from nature to create bio-inspired and biomimetic drug delivery platforms. Virus-like particles (VLPs) made from BIPs mimic the structure of viruses, enabling efficient drug delivery and immune modulation [176]. These systems can evade the immune system and target specific cells, improving therapeutic outcomes [177].

8.3 Artificial Intelligence (AI) in Drug Delivery Design

One exciting avenue for the future is the combination of BIP-based medication delivery systems with AI and machine intelligence. The design of BIP nanoparticles can be optimized using AI algorithms for targeted efficiency and particular drug release characteristics. AI predicts the best formulas and performance, which saves time and money when developing drug delivery systems [178].

8.4 Combination Therapies and Co-Delivery Systems

BIPs are being developed to enable the co-delivery of multiple therapeutic agents, such as drugs, genes, and imaging agents, for combination therapies. PLGA nanoparticles can simultaneously deliver chemotherapeutic drugs and siRNA to enhance cancer treatment efficacy. Co-delivery systems improve therapeutic outcomes by targeting multiple pathways and reducing drug resistance [179].

8.5 Sustainable and Biodegradable Implants

For long-term medication delivery, BIP-based implants that are completely biodegradable will be developed in the future. For prolonged medication release in orthopedic and cardiovascular applications, polycaprolactone (PCL) and polylactic acid (PLA) implants are being utilized. These implants deteriorate over time, removing the need for surgical removal and lowering patient suffering [180].

8.6 Nanotechnology and Advanced Fabrication Techniques

Advanced fabrication techniques, such as electrospinning and microfluidics, are being used to create BIP-based nanofibers and microspheres for drug delivery. Electrospun nanofibers made from gelatin and Chits are used for wound healing and localized drug delivery. These techniques enable precise control over the size, shape, and drug release properties of BIP-based systems [157].

9 Conclusion

Studies are still required to examine the ongoing and cost-effective environmental adjustments, even when the exceptional study on DDSs employing BIPs has transformed the pharmaceutical and medical industries. It has been shown that the BIPs found in produced DDSs are suitable and effective for a wide range of medical diseases. To improve biopotency, safety, and flexibility while avoiding contamination, however, research is currently ongoing to develop reliable standards for BIP applications. The same regime of requirements also includes studies on product loading capacity, metabolic activity, different encapsulation formulations, and technical parameter optimization.

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Chapter 7

Crosslinking Biopolymers and Its Clinical Applications

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Abstract Crosslinking of biopolymers has emerged as a critical strategy to enhance the structural integrity, mechanical strength, and functional performance of biomaterials, making them suitable for diverse clinical applications. Biopolymers, derived from natural sources such as polysaccharides, proteins, and nucleic acids, exhibit tremendous biocompatibility and biodegradability, rendering them ideal for biomedical use. However, their inherent limitations, including poor mechanical strength and rapid degradation, necessitate crosslinking to achieve desired physicochemical properties for specific medical applications. This chapter examines various crosslinking techniques, including physical, chemical, and hybrid methods, used to optimize biopolymer characteristics. The effects of crosslinking on the physicochemical properties of biopolymers, such as mechanical stability, swelling behavior, and degradation profiles, are systematically analyzed. A comprehensive overview

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of the clinical applications of crosslinked biopolymers is provided, focusing on drug delivery systems, wound healing, tissue engineering scaffolds, orthopedic implants, and cardiovascular devices. The chapter highlights the role of crosslinking in enabling controlled drug release, improving cellular interactions, and enhancing implant longevity. Additionally, emerging smart biopolymer systems that respond to environmental stimuli such as pH, temperature, and enzymes are discussed as promising innovations. Challenges associated with crosslinking, such as cytotoxicity, regulatory issues, and scalability, are addressed. The chapter also explores recent advancements in bioinspired and green crosslinking techniques aimed at improving biocompatibility and minimize toxic by-products. Overall, this chapter provides valuable insights into the principles of crosslinked biopolymers and their transformative potential in modern healthcare, driving future developments in biomaterials and regenerative medicine.

Keywords Biopolymers · Crosslinking · Biomaterials · Cardiovascular devices · Tissue engineering scaffolds · Drug release

1 Introduction

1.1 Definition and Significance of Biopolymer Crosslinking

Biopolymers are naturally occurring macromolecules synthesized by living organisms (1), comprising long chains of repeating monomeric units (2). Examples include polysaccharides, proteins, and nucleic acids [1, 2]. These materials are inherently biodegradable, biocompatible, and sustainable, making them ideal candidates for biomedical applications (3). Biopolymers have gained significant attention in recent years due to their potential in providing sustainable and biodegradable alternatives across a wide range of applications [3, 4]. In the field of drug delivery, these materials play a vital role in enhancing the therapeutic efficacy of bioactive compounds, making them a key component in modern treatment strategies. Polymers derived from synthetic, natural, and semi-synthetic sources are frequently used in the development of drug delivery systems [5, 6]. However, the extensive use of synthetic and chemically derived polymers, particularly in the food and medical sectors, has raised environmental concerns. Growing awareness around sustainability, stricter regulations on pollution, and the need for better waste management have accelerated the shift toward biopolymer-based solutions. These eco-friendly materials help reduce carbon emissions, decrease municipal waste, and lessen dependence on fossil fuel-derived resources [7, 8].

Crosslinking is a chemical or physical process in which two or more polymer chains are joined together via covalent or non-covalent bonds, resulting in a three-dimensional network [9]. This process significantly enhances the mechanical, thermal, and chemical properties of biopolymers, making them more suitable for

a wide range of clinical and industrial applications. Crosslinking can improve the rigidity, elasticity, water retention capacity, and resistance to enzymatic degradation of biopolymers, thereby expanding their utility in biomedical engineering, drug delivery, wound healing, and tissue scaffolding [10]. In clinical contexts, crosslinked biopolymers are often tailored to mimic the extracellular matrix (ECM), providing structural support and biological signals essential for cellular adhesion, proliferation, and differentiation. As a result, the crosslinking of biopolymers plays a pivotal role in enhancing their functional and structural integrity for diverse medical uses [11].

2 Overview of Biopolymers: Polysaccharides, Proteins, and Nucleic Acids

Biopolymers are natural macromolecules synthesized by living organisms and are composed of repeating monomeric units [12]. They are biodegradable, biocompatible, and often exhibit inherent bioactivity, making them highly desirable for various biomedical and clinical applications [7, 13]. Biopolymers can be broadly categorized into three main classes based on their chemical nature and biological origin: polysaccharides, proteins, and nucleic acids [7, 12]. Each class possesses distinct physicochemical properties, advantages, and limitations that influence their use in biomedicine—particularly in the context of crosslinking for functional material development.

Biopolymers can be broadly categorized based on their origin and monomeric composition:

i. Polysaccharides

Polysaccharides are **carbohydrate-based polymers** composed of monosaccharide units linked by glycosidic bonds. They can be either **homopolysaccharides** (made of one type of monosaccharide) or **heteropolysaccharides** (containing different types of monosaccharides). These naturally occurring biopolymers are abundantly found in plant, animal, algal, and microbial sources [14].

Examples of Common Polysaccharides :

- **Chitosan:** Derived from the deacetylation of chitin, it is widely used in drug delivery, wound healing, and tissue engineering due to its antimicrobial, biodegradable, and bioadhesive properties [15].
- **Alginate:** Extracted from brown seaweed, alginate forms hydrogels in the presence of divalent cations like calcium. It is used in wound dressings, cell encapsulation, and as a scaffold material [16].
- **Hyaluronic Acid (HA):** A major component of the extracellular matrix (ECM), HA is involved in cell signaling, wound healing, and tissue hydration. It is commonly used in ophthalmic surgery, joint therapies, and cosmetic fillers.

- **Cellulose:** The most abundant natural polymer, cellulose has excellent mechanical strength but is insoluble in water. Its derivatives (e.g., hydroxypropyl cellulose) are often used in biomedical formulations [17].
- **Dextran:** A branched polysaccharide produced by bacterial fermentation, dextran is used as a plasma volume expander, in drug delivery, and as a component in hydrogels [18].

Advantages of Polysaccharides [14]:

- High biocompatibility and low immunogenicity
- Biodegradability and environmental sustainability
- Easily modifiable functional groups (e.g., hydroxyl, carboxyl, amine)

Crosslinking improves their mechanical integrity, stability, and functionality, making them more suitable for **long-term biomedical applications** such as implantable scaffolds, wound dressings, and drug delivery matrices [19].

ii. Proteins

Protein-based biopolymers are composed of **amino acid sequences** and exhibit diverse and tunable biological properties due to their inherent structural complexity. As natural components of the extracellular matrix and other bodily systems, proteins play a vital role in **cellular communication, adhesion, proliferation, and differentiation** [20–22].

Examples of Protein-Based Biopolymers:

- **Collagen:** Being the most abundant structural protein in mammals, collagen forms triple-helical fibrils and provides mechanical support in connective tissues. It is widely used in wound healing, tissue engineering, and cosmetic products [23–25].
- **Gelatin:** Gelatin, a denatured form of collagen, is soluble in water and forms thermally reversible gels. It is extensively used in drug delivery systems and injectable hydrogels [26, 27].
- **Silk Fibroin:** Obtained from the silkworm (*Bombyx mori*), it is known for its exceptional mechanical strength, biocompatibility, and controlled biodegradation.
- **Elastin:** This protein provides elasticity to tissues such as skin, lungs, and blood vessels. Its degradation or absence is linked to aging and various pathologies [28, 29].
- **Fibrin:** Formed from fibrinogen during blood clotting, it forms a natural matrix that supports tissue regeneration. It is commonly used in fibrin sealants and tissue adhesives [30–32].

Advantages of Protein Biopolymers [33–35]:

- Excellent bioactivity and cell-interactive properties
- Ability to mimic natural ECM structure
- Biodegradable and metabolizable by natural processes

Crosslinking of proteins helps to **stabilize their structure**, prolong their in vivo lifespan, and control their degradation rate. Chemical crosslinkers such as glutaraldehyde or enzymatic agents like transglutaminase are commonly used to enhance the performance of protein-based biomaterials [36].

iii. Nucleic Acids

Nucleic acids, including **DNA (deoxyribonucleic acid)** and **RNA (ribonucleic acid)**, are biopolymers composed of nucleotide monomers (adenine, guanine, cytosine, thymine/uracil). While traditionally recognized for their role in **genetic information storage and transmission**, nucleic acids have recently gained attention as **functional materials** in nanomedicine and biotechnology due to their unique structural and self-assembly capabilities [37, 38].

3 Applications of Nucleic Acid Biopolymers:

- **DNA Hydrogels:** Networks formed from DNA strands capable of encapsulating drugs or cells for controlled release or diagnostic purposes [39, 40].
- **RNA-based Therapeutics:** siRNA, mRNA, and aptamers are used for gene silencing, protein expression, and targeted drug delivery [41, 42].
- **Biosensors:** DNA and RNA aptamers are used in sensors for detecting pathogens, toxins, and small molecules [43, 44].

4 Advantages [38, 45]:

- Programmability at the molecular level
- High specificity and structural predictability
- Ability to undergo self-assembly and hybridization

Through **chemical or enzymatic crosslinking**, nucleic acids can be transformed into **stable, functional materials** such as **stimuli-responsive hydrogels** or **nanos-structures** for therapeutic delivery. These systems are particularly promising in **gene therapy, cancer treatment, and biosensing platforms** [45–47].

5 Importance of Crosslinking in Biomedical Advancements

The strategic application of crosslinking in biopolymer engineering has led to significant breakthroughs in biomedical sciences [48–50]:

- **Tissue Engineering:** Crosslinked biopolymers serve as scaffolds that support cell growth and tissue regeneration. For example, crosslinked collagen or hyaluronic acid hydrogels are used in cartilage repair and dermal regeneration [51].
- **Drug Delivery Systems:** Crosslinking allows for the design of **controlled-release matrices** where therapeutic agents are released in a sustained and targeted manner, improving treatment efficacy and reducing side effects [52, 53].
- **Wound Healing:** Crosslinked biopolymer films and gels maintain a moist wound environment, protect against microbial invasion, and promote faster healing [54, 55].
- **Biosensors and Diagnostics:** DNA-based crosslinked hydrogels are used in responsive biosensing platforms, capable of detecting specific biological molecules with high sensitivity and selectivity [49, 56].
- **Injectable Hydrogels:** In situ-forming crosslinked hydrogels can be injected into target sites, solidifying under physiological conditions to act as delivery systems, fillers, or structural supports [36, 57].
- **Dental and Orthopedic Materials:** Crosslinked alginates and chitosan have shown promise in bone regeneration and as bio-adhesives in dental surgery [58–60].

Crosslinking, thus, transforms biopolymers into **high-performance biomaterials**, enabling their integration into advanced medical technologies and improving patient outcomes [10]. The future of biopolymer research lies in the development of **smart, stimuli-responsive crosslinked systems** capable of adapting to dynamic physiological environments and delivering personalized therapeutic effects [61–63].

6 Crosslinking Techniques for Biopolymers

6.1 Physical Crosslinking

Physical crosslinking of biopolymers involves the establishment of non-covalent interactions that induce three-dimensional network formation without the use of chemical crosslinkers [64, 65]. These mechanisms include ionic interactions [64], hydrogen bonding, irradiation-induced free-radical formation [64, 66, 67], and freeze-thaw-induced crystallinity [68–70]. Each technique offers unique physico-chemical properties and processing advantages relevant to biomedical, pharmaceutical, and environmental applications (Table 1).

Ionic Interactions: Calcium Ion Crosslinking in Alginate Hydrogels

Alginate is an anionic polysaccharide primarily composed of β -D-mannuronic acid (M) and α -L-guluronic acid (G) residues [68, 71, 72]. The G-blocks of alginate exhibit high affinity for divalent cations such as Ca^{2+} [71]. Upon exposure to Ca^{2+} ions, the G-blocks align and form junction zones via ionic coordination, often described by the “egg-box” model [73]. This rapid gelation process occurs under ambient

Table 1 Summary of crosslinking techniques for biopolymers

Crosslinking type	Method	Mechanism	Materials involved	Key features/Applications
Physical	Ionic interactions	Ionic bonding between alginate G-blocks and Ca^{2+} ions	Alginate, Ca^{2+}	Rapid gelation, tunable properties, biocompatibility, sensitive to ion exchange
	Hydrogen bonding	Intra/intermolecular H-bonds between polar groups	Cellulose, chitosan, starch	Enhances crystallinity, reversible, stimuli-responsive, self-healing materials
	UV/Gamma irradiation	Free radical formation via photoinitiators or radiolysis	PVA, gelatin, polyethylene oxide	Sterilization, 3D printing, solvent-free, potential degradation with overexposure
	Freeze–thaw cycles	Ice crystallization and polymer chain entanglement	PVA, gelatin-PVA, chitosan-PVA	Non-toxic, scalable, high mechanical strength, used in biosensors & drug delivery
Chemical	Glutaraldehyde Crosslinking	Covalent imine bond formation with amines	Proteins, polysaccharides	Strong, efficient, potential cytotoxicity
	Genipin crosslinking	Covalent reaction with primary amines	Collagen, chitosan	Low toxicity, biocompatible, elastic networks
	EDC/NHS carbodiimide	Amide bond formation (zero-length crosslinker)	Collagen, gelatin, hyaluronic acid	No residue, widely used in biomedical modification
	Enzymatic (Transglutaminase)	ϵ -(γ -glutamyl)lysine bond formation	Proteins	Biocompatible hydrogels, food and wound healing applications
	Enzymatic (Lysyl oxidase)	Oxidative deamination leading to crosslinks	Collagen, elastin	ECM mimicry, mechanical enhancement in scaffolds

(continued)

Table 1 (continued)

Crosslinking type	Method	Mechanism	Materials involved	Key features/Applications
	Click chemistry	Azide-alkyne cycloaddition (CuAAC, SPAAC)	Functionalized biopolymers	Modular, bioorthogonal, used in drug delivery and hydrogels
	Schiff base formation	Aldehyde-amine condensation forming imines/hydrazones	Aldehyde/amine-functionalized polymers	Reversible, injectable, pH-responsive hydrogels

conditions, with the degree of crosslinking modulated by the Ca^{2+} concentration, alginate molecular weight, and G/M ratio [73, 74].

Calcium-crosslinked alginate hydrogels are characterized by high water content, tunable mechanical properties, and biocompatibility. However, ion exchange with monovalent cations in physiological fluids may lead to structural instability [75–77]. To address this, secondary crosslinking or incorporation of reinforcing agents (e.g., nanoparticles, co-polymers) is commonly employed.

Hydrogen Bonding: Stabilization of Polysaccharide-Based Scaffolds

Hydrogen bonding is a fundamental interaction contributing to the structural integrity of polysaccharide-based matrices [78, 79]. Hydroxyl, carboxyl, and amino functional groups present in polymers such as cellulose, chitosan, and starch can form extensive intra- and intermolecular hydrogen bonds [80–84]. These interactions are highly dependent on factors including temperature, hydration level, and polymer chain mobility.

In solid-state and semi-solid matrices, hydrogen bonding enhances crystallinity and mechanical strength. This mechanism is critical in the fabrication of aerogels, xerogels, and dry films [85, 86]. Furthermore, the reversibility of hydrogen bonds under external stimuli (e.g., pH, ionic strength) enables the design of smart, stimuli-responsive materials [87, 88]. Recent developments in supramolecular assembly leverage directional hydrogen bonding to engineer self-healing and shape-memory biomaterials [89].

UV and Gamma Irradiation: Induction of Crosslinks Through Free-Radical Formation

Irradiation-induced crosslinking involves the generation of reactive species (typically free radicals) that facilitate polymer chain interlinking [90, 91]. UV radiation, in the presence of photoinitiators (e.g., Irgacure compounds), initiates radical polymerization in acrylate- or methacrylate-functionalized biopolymers [92–94]. This method allows spatial and temporal control over network formation and is widely used in photolithography and 3D bioprinting.

Gamma irradiation, characterized by deep penetration and uniform energy distribution, initiates crosslinking via water radiolysis and direct excitation of polymer chains [95, 96]. It is particularly effective for sterilizing and crosslinking bulk materials such as polyvinyl alcohol, gelatin, and polyethylene oxide [97–99]. However, overexposure can result in chain scission and material degradation, necessitating optimization of radiation dose.

Applications include the fabrication of sterilized hydrogel dressings, biore-sorbable scaffolds, and composite membranes. The ability to process without solvents or chemical reagents makes irradiation a favorable method for medical-grade biomaterials [100, 101].

Freeze–Thaw Cycles: Strengthening Polymer Networks in Hydrogels

The freeze–thaw method exploits phase separation induced by ice crystallization to drive polymer chain alignment and crystallite formation [70, 102]. Upon freezing,

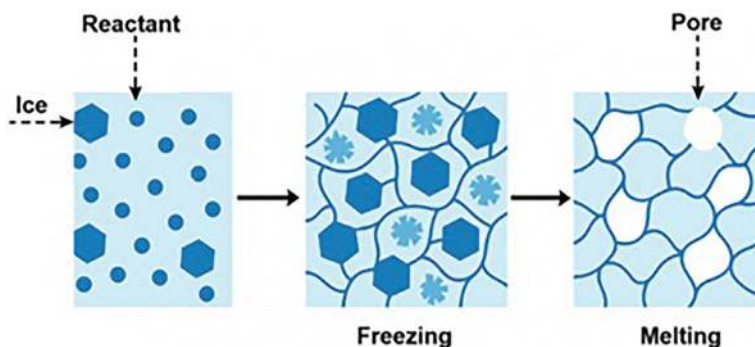


Fig. 1 Schematic representation of the cryogelation process. This figure illustrates the cryogelation process in three stages: (1) **Reactant + Freezing**, where reactants and ice crystals form in a pre-gel solution; (2) **Cryogel Formation**, as polymer chains crosslink around the frozen solvent; and (3) **Thawing**, where ice melts, leaving behind an interconnected porous structure ideal for biomedical application

solvent exclusion concentrates polymer chains, promoting hydrogen bonding and crystallization [103, 104]. Thawing retains these interactions as permanent physical crosslinking points [105]. Repeated cycles enhance crystallinity and interchain entanglements [106] (Fig. 1).

Polyvinyl alcohol (PVA) is the prototypical polymer for freeze–thaw-induced gelation, forming robust hydrogels with high elasticity and water content [99]. Natural polymer blends, including gelatin–PVA or chitosan–PVA systems, benefit from this approach by improving mechanical properties and gel stability without chemical modification [107, 108].

Freeze–thaw processing is solvent-free, non-toxic, and scalable, making it highly applicable in tissue engineering, biosensor substrates, and drug delivery matrices [109, 110]. Recent studies have combined freeze–thaw cycling with reinforcing fillers or nanoparticles to achieve hierarchical network structures with superior functional performance [111].

Physical crosslinking methods provide a versatile platform for the fabrication of biopolymer-based materials with tailored properties. Ionic coordination, hydrogen bonding, irradiation-induced radical formation, and freeze–thaw cycling each confer distinct mechanical, thermal, and environmental responses. A deep understanding of these mechanisms is essential for optimizing material design in applications such as regenerative medicine, controlled release systems, and bioactive coatings. Ongoing innovations aim to integrate multiple crosslinking modes to achieve hybrid networks with synergistic performance characteristics.

6.2 Chemical Crosslinking

Chemical crosslinking involves the formation of covalent bonds between polymer chains, resulting in stable, often irreversible three-dimensional networks [112–114]. This strategy allows precise control over the structural and mechanical properties of biopolymeric materials and can be tailored to meet specific application requirements [115, 116]. Common chemical crosslinking approaches include the use of synthetic or naturally derived crosslinkers, enzyme-mediated bonding, and orthogonal chemistries such as click reactions and Schiff base formation [117–119] (Table 1).

Covalent Bonding Using Crosslinkers: Glutaraldehyde, Genipin, Carbodiimides (EDC/NHS)

Covalent crosslinking using small molecule crosslinkers is a well-established method to enhance the mechanical strength, thermal stability, and durability of biopolymeric networks [120].

- **Glutaraldehyde** is a bifunctional aldehyde that reacts with amine groups on proteins and polysaccharides to form stable imine bonds. It is widely used due to its rapid reaction kinetics and efficiency; however, concerns regarding cytotoxicity and residual crosslinker necessitate careful control and post-treatment [120–122].
- **Genipin**, a naturally derived crosslinker from Gardenia fruits, also reacts with primary amines to form stable crosslinks. Compared to glutaraldehyde, genipin exhibits significantly lower cytotoxicity and produces crosslinked networks with enhanced elasticity and biocompatibility. It is particularly favored in tissue engineering and regenerative medicine [123].
- **Carbodiimide chemistry**, typically employing 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) in combination with N-hydroxysuccinimide (NHS), facilitates the formation of amide bonds between carboxyl and amine groups [124]. This zero-length crosslinking method avoids introducing foreign residues into the final network and is commonly used to modify collagen, gelatin, and hyaluronic acid [125] Fig. 2.

Enzyme-Mediated Crosslinking: Transglutaminase, Lysyl Oxidase

Enzymatic crosslinking offers high specificity under physiological conditions, making it ideal for in vivo applications and biomaterial fabrication involving sensitive bioactive components [126, 127].

- **Transglutaminase** catalyzes the formation of ϵ -(γ -glutamyl)lysine bonds between glutamine and lysine residues in proteins [128]. This method produces biocompatible, enzymatically crosslinked hydrogels suitable for wound healing, food biopolymers, and tissue scaffolds.
- **Lysyl oxidase (LOX)** initiates oxidative deamination of lysine residues, leading to covalent crosslinking in extracellular matrix components such as collagen and elastin [129]. LOX-based crosslinking strategies are under exploration for

Small Molecule Crosslinkers

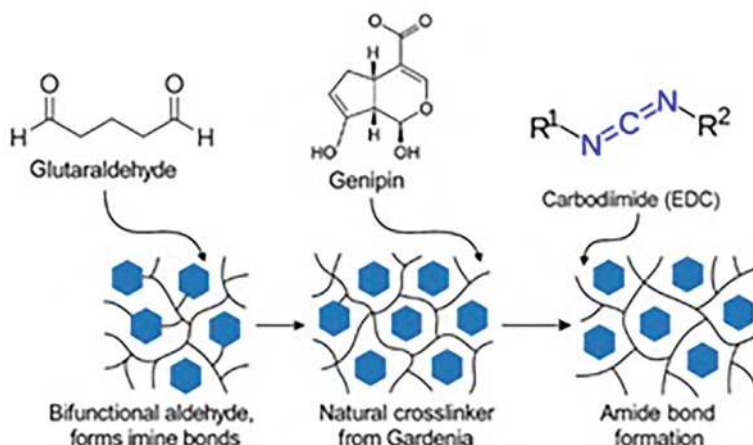


Fig. 2 Common small molecule crosslinkers and their mechanisms in biomaterials. This figure illustrates three small molecule crosslinkers: (1) Glutaraldehyde, a bifunctional aldehyde forming imine bonds; (2) Genipin, a natural crosslinker from Gardenia forming stable networks; and (3) Carbodiimide (EDC), promoting amide bond formation between carboxyl and amine groups

mimicking native tissue architecture in bioengineered scaffolds and enhancing mechanical resilience [130].

These enzymes allow spatial and temporal control of crosslinking through the regulation of enzyme concentration and activation conditions.

Click Chemistry and Schiff Base Reactions: Highly Selective, Biocompatible Modifications

Orthogonal chemistries such as click reactions and Schiff base formation provide high efficiency and selectivity in crosslinking biopolymers under mild conditions [131, 132].

- **Click chemistry**, particularly azide-alkyne cycloaddition (CuAAC or strain-promoted SPAAC), enables modular assembly of polymer networks with excellent control and minimal by-products. This reaction is bioorthogonal, proceeding without interfering with native biological processes, and is widely used in hydrogel formation, drug delivery vehicles, and surface functionalization [131, 133–135].
- **Schiff base reactions**, involving the condensation of aldehydes with primary amines to form imine or hydrazone linkages, offer a reversible or dynamic crosslinking mechanism depending on pH and environmental conditions. These reactions are especially useful for forming injectable hydrogels, self-healing systems, and pH-responsive materials [117].

The versatility of these chemistries allows for customization of mechanical properties, degradation profiles, and biofunctionality, supporting advanced biomedical applications such as stimuli-responsive scaffolds and targeted delivery systems [136].

Chemical crosslinking techniques afford robust and tunable polymer networks suitable for diverse biomedical and industrial uses [112, 118, 119]. Covalent crosslinking with bifunctional agents, enzymatic catalysis, and orthogonal chemistries each offer unique advantages in terms of reaction specificity, biocompatibility, and application versatility [137]. Integrating chemical crosslinking strategies with smart design principles is key to advancing next-generation biomaterials with tailored functionalities.

7 Clinical Applications of Crosslinked Biopolymers

7.1 Drug Delivery Systems

Crosslinked biopolymers are integral to the design of advanced drug delivery systems due to their tunable mechanical strength, degradation rates, and biore sponsiveness [65, 118, 120]. Their ability to encapsulate therapeutic agents and control release kinetics enables localized, sustained, and stimuli-responsive delivery, reducing systemic side effects and improving treatment efficacy [138]. In particular, crosslinked systems offer spatial and temporal control over drug release, which is crucial for achieving therapeutic concentrations at target sites while avoiding drug accumulation in healthy tissues [139] (Table 2).

Controlled Drug Release via Crosslinked Hydrogels

Hydrogels formed from chemically or physically crosslinked biopolymers can retain large amounts of water, allowing for the incorporation and sustained release of hydrophilic and hydrophobic drugs [84, 114, 122, 126]. The degree of crosslinking directly influences the porosity, swelling ratio, and diffusion properties of the hydrogel matrix, which in turn governs the release profile. Common materials include alginate, chitosan, gelatin, hyaluronic acid, and polyethylene glycol derivatives [75, 82, 96, 125]

Controlled drug release from hydrogels is widely applied in wound healing, cancer therapy, ocular drug delivery, and chronic disease management [139–143]. For instance, crosslinked gelatin or PEG-based hydrogels can deliver chemotherapeutics or growth factors at defined rates, improving patient compliance and therapeutic outcomes [144, 145]. Furthermore, multi-layer or gradient hydrogels can be engineered to release multiple agents sequentially, mimicking complex biological healing processes [146, 147].

Innovations in hydrogel design also include thermoresponsive, magnetic, and ultrasound-sensitive systems that offer external control over drug release kinetics, enabling patient-specific treatment protocols [148–150].

Table 2 Summary of clinical applications of crosslinked biopolymers

Section	Subcategory	Key features/Applications
Drug delivery systems	Controlled drug release via crosslinked hydrogels	Hydrophilic/hydrophobic drug loading, tunable release via porosity/swelling; used in cancer, wound care, ocular delivery
	Nanoparticle-embedded biopolymer matrices	Dual-level control, active targeting, sequential release; used in chemotherapy, gene therapy
	pH-responsive and enzyme-degradable systems	Responsive to pH/enzymes, site-specific release, tailored degradation; oral delivery, cancer therapy
Wound healing and tissue engineering	Hydrogels for chronic wound dressings	Maintain hydration, load bioactive agents, stimuli-responsive; diabetic ulcers, burns
	Collagen/chitosan scaffolds for skin regeneration	Support fibroblasts, angiogenesis; genipin or EDC/NHS crosslinking; used in grafts, substitutes
	Smart biomaterials with antimicrobial/Angiogenic activity	Release antimicrobial/angiogenic agents on cue; ROS-scavenging, oxygenating; real-time sensing
Orthopedic and dental applications	Bone graft substitutes with mineralization	Chitosan/collagen with HA/TCP; osteoinductive molecule delivery; used in craniofacial, long bone defects
	Injectable hydrogels for cartilage repair	Minimally invasive, encapsulate cells/growth factors, responsive properties
	Biopolymer-based dental adhesives and membranes	Improved adhesion, antimicrobial protection, used in periodontal regeneration
Cardiovascular applications	Biopolymer-coated stents	Reduce thrombosis, sustain drug release, endothelial compatibility; RGD peptide functionalization
	Crosslinked vascular grafts	Enhanced compliance, NO-releasing, mimic native vessels; made with ECM, elastin
	Heart valve replacements	Reduced calcification, dynamic crosslinking, seeded scaffolds; TAVR, pediatric valves

Nanoparticle-Embedded Biopolymer Matrices for Targeted Therapies

Incorporating drug-loaded nanoparticles into crosslinked biopolymer matrices enables dual-level control over drug release and targeting [151, 152]. Nanoparticles such as liposomes, polymeric nanospheres, dendrimers, or metallic nanoparticles (e.g., gold, silver, iron oxide) can be embedded in a hydrogel or film, offering protection for sensitive drug molecules and facilitating targeted delivery to specific tissues or cell types [153, 154].

These hybrid systems allow sequential or controlled burst release strategies, where nanoparticles offer initial release or cell-specific uptake, followed by prolonged release from the surrounding matrix [155, 156]. By surface-modifying nanoparticles with ligands such as antibodies or peptides, active targeting to diseased tissues, including tumors and inflamed sites, can be achieved [157].

Applications include localized chemotherapy, immunotherapy, and gene delivery. For example, siRNA-loaded nanoparticles embedded in enzymatically crosslinked gelatin hydrogels have been shown to suppress gene expression in localized tumors, demonstrating the therapeutic potential of these constructs [158].

pH-Responsive and Enzyme-Degradable Biopolymers

Stimuli-responsive crosslinked biopolymers can respond to environmental cues such as pH, temperature, or enzymatic activity, enabling site-specific and condition-triggered drug release [159, 160].

- **pH-responsive systems** exploit differences in physiological pH across tissues (e.g., acidic tumor microenvironments, inflamed tissues, or gastric vs. intestinal pH gradients) [159]. Materials such as chitosan, polyacrylic acid, poly- β -amino esters, and zwitterionic polymers swell or degrade in response to pH changes, allowing for tailored drug delivery profiles [82, 96, 108, 152, 161]. These systems are extensively investigated for oral delivery of acid-labile therapeutics and site-specific cancer treatments.
- **Enzyme-degradable systems** utilize natural or engineered biopolymers that are cleaved by disease-associated enzymes. Matrix metalloproteinases (MMPs), elastase, and lysozyme are common targets for responsive degradation [162, 163]. For example, MMP-sensitive peptide crosslinkers incorporated into PEG hydrogels enable controlled degradation in tumor microenvironments, releasing chemotherapeutics only at the site of disease [164].

Advanced designs have combined multiple stimuli-responsiveness (e.g., pH and enzyme) into a single platform, enhancing specificity and minimizing off-target effects [165]. Such systems are under clinical investigation for site-specific delivery of biologics, anti-inflammatory agents, and combination therapies [166, 167].

Crosslinked biopolymers offer a versatile platform for designing advanced drug delivery systems that combine controlled release, targeted delivery, and environmental responsiveness. Their structural adaptability, biocompatibility, and capacity for functional modification make them key enablers of precision medicine and next-generation therapeutics. As research progresses, integration with digital health

technologies and responsive diagnostics may further enhance the performance and personalization of crosslinked drug delivery systems, transforming therapeutic strategies across clinical disciplines.

7.2 Wound Healing and Tissue Engineering

Crosslinked biopolymers are pivotal in the development of wound dressings and tissue scaffolds due to their biocompatibility, biodegradability, and capacity for structural customization [168]. These materials support cellular adhesion, proliferation, and differentiation while protecting the wound site and facilitating tissue repair. The ability to fine-tune their mechanical strength, porosity, and degradation rate via crosslinking enables the design of tailored solutions for both acute and chronic wounds, as well as tissue regeneration applications.

Hydrogels for Chronic Wound Dressings

Hydrogels formed from crosslinked natural polymers such as alginate, gelatin, hyaluronic acid, and cellulose derivatives offer an ideal moist environment for wound healing [168–170]. Their high-water content maintains hydration at the wound site, promotes autolytic debridement, and enhances patient comfort. Crosslinking imparts structural stability and allows controlled swelling, drug release, and biodegradation.

In chronic wound care (e.g., diabetic ulcers, pressure sores), hydrogel dressings can be loaded with antimicrobial agents, growth factors, or anti-inflammatory drugs to manage infection and stimulate healing [171]. Thermoresponsive and pH-sensitive hydrogel systems have also been developed for on-demand drug release in response to the wound microenvironment [152].

Recent developments have focused on hydrogel composites that incorporate nanofillers such as graphene oxide, silica nanoparticles, or clay platelets [172, 173]. These additives improve mechanical strength, enhance antibacterial activity, and offer stimuli-responsive behavior, further expanding their clinical potential. Additionally, photo-crosslinkable hydrogels using UV or visible light allow in situ formation directly at the wound site, enabling patient-specific application and minimizing handling [174].

Crosslinked Collagen and Chitosan Scaffolds for Skin Regeneration

Collagen and chitosan are two of the most studied biopolymers in skin regeneration due to their inherent bioactivity and compatibility with skin tissue [175–177]. Chemical crosslinking with agents such as genipin or EDC/NHS enhances their mechanical integrity and degradation resistance while maintaining a conducive environment for cell attachment and growth [178].

- Crosslinked collagen scaffolds mimic the native extracellular matrix (ECM), supporting fibroblast migration, angiogenesis, and epidermal layer formation. These scaffolds are widely used in dermal substitutes and skin grafts [179].

- Chitosan-based scaffolds, owing to their intrinsic antimicrobial properties and hemostatic activity, are effective in preventing wound infection and promoting tissue granulation [180]. Crosslinking improves their mechanical performance and allows tuning of degradation rates to match tissue repair timelines.

Blending collagen and chitosan, or incorporating other ECM components like elastin or glycosaminoglycans, further enhances scaffold functionality and biocompatibility [181].

Advanced approaches include incorporating stem cells, platelet-rich plasma (PRP), or exosomes into crosslinked scaffolds to boost regenerative signaling and accelerate healing [182–185]. Bioprinted scaffolds with spatially defined gradients of cells and growth factors are being developed to recreate skin architecture more precisely and improve integration with surrounding tissues [186].

Smart Biomaterials with Antimicrobial and Angiogenic Properties

Next-generation wound healing materials incorporate bioresponsive elements that can actively participate in the healing process [187]. These smart biomaterials are designed to release antimicrobial peptides, nitric oxide, or metal ions (e.g., silver, zinc) in response to infection or pH changes [188, 189].

Angiogenic factors such as vascular endothelial growth factor (VEGF) or stromal cell-derived factor-1 (SDF-1) can be encapsulated within the crosslinked network and released in a controlled manner to stimulate new blood vessel formation, a critical aspect of tissue regeneration [190].

Incorporation of reactive oxygen species (ROS)-scavenging components, oxygen-releasing compounds, and bioelectric cues into crosslinked biopolymers is also being explored. These additions enhance wound oxygenation, reduce inflammation, and promote tissue granulation [191, 192].

Additionally, electrospun fiber mats, 3D bioprinted scaffolds, and stimuli-responsive hydrogels are being integrated with crosslinked biopolymer systems to create multifunctional dressings that adapt dynamically to the wound environment [193–195]. Smart scaffolds capable of real-time wound monitoring through embedded sensors or colorimetric indicators are under development, bringing the field closer to precision-guided wound management.

Crosslinked biopolymers offer a powerful toolkit for developing advanced wound healing and tissue engineering platforms [121, 196]. Their tunable physical and biochemical properties enable precise control over cellular interactions, degradation kinetics, and therapeutic delivery [197]. Continued innovation in scaffold design, bioactive incorporation, and smart functionality will drive the next generation of regenerative medical products for skin and soft tissue repair [100, 183, 198–200]. Future directions include the integration of crosslinked systems with wearable technologies, personalized medicine approaches, and advanced manufacturing techniques such as 4D bioprinting to achieve dynamic, patient-specific wound care solutions.

7.3 *Orthopedic and Dental Applications*

Crosslinked biopolymers have gained substantial interest in orthopedic and dental applications due to their tunable mechanical properties, bioactivity, and structural similarity to native extracellular matrices (ECMs) [201]. These systems can be engineered to enhance osteointegration, chondrogenesis, and periodontal regeneration, offering bioresorbable, functional alternatives to inert implants and synthetic composites [202].

Bone Graft Substitutes with Enhanced Mineralization

Bone graft substitutes constructed from crosslinked biopolymer matrices are employed to address critical-size defects and promote bone regeneration through osteoconductive and osteoinductive mechanisms [158, 198–200, 203, 204]. Collagen, gelatin, chitosan, and alginate are frequently used as scaffolding materials due to their biodegradability and affinity for mineral deposition [75, 82, 107, 120, 125, 145, 152, 177, 181, 205]. These polymers are often reinforced with inorganic fillers such as hydroxyapatite (HA), tricalcium phosphate (TCP), calcium sulfate, or bioactive glass to enhance mechanical strength and mimic the mineral phase of bone [206].

Chemical crosslinking using agents like genipin, glutaraldehyde, or EDC/NHS improves the compressive strength, structural retention, and enzymatic resistance of the scaffold [120, 121, 207]. The incorporation of osteoinductive molecules such as bone morphogenetic proteins (BMP-2 or BMP-7), vascular endothelial growth factor (VEGF), or transforming growth factor-beta (TGF- β) further stimulates mesenchymal stem cell (MSC) differentiation and neovascularization at the defect site [125, 190].

Advanced fabrication techniques, including 3D printing, electrospinning, and freeze-drying, enable spatial patterning of porosity and mechanical gradients, allowing better integration with host bone and facilitating nutrient diffusion and vascular ingrowth [68, 69, 198]. These crosslinked constructs are being actively explored in orthopedic indications such as vertebral fusion, long bone defect repair, craniofacial reconstruction, and load-bearing applications.

Injectable Hydrogels for Cartilage Repair

Due to the avascular and aneural nature of cartilage, intrinsic self-healing is limited, necessitating the use of exogenous biomaterials to promote regeneration [208]. Injectable hydrogels derived from crosslinked biopolymers such as hyaluronic acid, gelatin methacryloyl (GelMA), alginate, and chitosan provide a minimally invasive approach to fill chondral defects and deliver therapeutic agents or cells directly to the site of injury [140].

Crosslinking modalities including photopolymerization (e.g., with visible or UV light and photoinitiators like LAP or Irgacure), enzyme-mediated reactions (e.g., using horseradish peroxidase or transglutaminase), or click chemistry (e.g., thiol-ene or azide-alkyne cycloaddition) ensure in situ gelation and retention within the

joint cavity [209]. These methods allow for tunable viscoelastic properties that mimic native cartilage, supporting load-bearing function and matrix remodeling.

Hydrogels can be functionalized with chondrogenic factors such as TGF- β 1, insulin-like growth factor (IGF-1), or Sox9 peptides, and may encapsulate chondrocytes or mesenchymal stem cells to enhance neocartilage formation [210]. Emerging approaches include magneto-responsive and thermogelling systems that enable external modulation of scaffold behavior and controlled release of therapeutic agents.

Biopolymer-Based Dental Adhesives and Membranes

In restorative and regenerative dentistry, crosslinked biopolymers are utilized to improve bonding interfaces, regenerate periodontal structures, and prevent microbial invasion. Dental adhesives composed of gelatin, dextran, or polyacrylic acid matrices crosslinked with carbodiimide or aldehyde chemistry exhibit improved cohesive strength, wettability, and interfacial adhesion to dentin substrates [96, 106, 107, 125, 145, 162].

Guided tissue regeneration (GTR) and guided bone regeneration (GBR) employ crosslinked collagen, chitosan, or polylactic acid membranes to selectively exclude epithelial cell migration while providing a scaffold for osteogenic and fibroblastic proliferation [211]. Crosslinking enhances the durability and resorption kinetics of these membranes, which can be tailored to match the healing rate of specific periodontal sites.

Incorporation of antibacterial agents such as chlorhexidine, silver nanoparticles, or bioactive glass imparts antimicrobial protection against oral pathogens [212–214]. Additionally, bioresponsive systems capable of releasing drugs in response to bacterial enzymes or pH shifts offer intelligent control over localized therapy, particularly in infected or inflamed environments.

Recent innovations include photo-crosslinkable dental composites, injectable regenerative gels, and electrospun biopolymer mats designed to integrate with root canals, periodontal pockets, and alveolar bone interfaces [215, 216].

Crosslinked biopolymers offer a versatile and adaptive platform for orthopedic and dental applications. Their customizable mechanical, chemical, and biological profiles enable the fabrication of advanced biomaterials tailored to support bone and soft tissue repair, cartilage regeneration, and oral tissue reconstruction. Future research is focused on integrating growth factor gradients, smart bioresponsive elements, and high-resolution fabrication methods to achieve next-generation solutions in musculoskeletal and dental regenerative medicine.

7.4 Cardiovascular Applications

Crosslinked biopolymers play a crucial role in the advancement of cardiovascular biomaterials by offering tailored mechanical, structural, and biochemical properties that more closely emulate native tissues than traditional metallic or

synthetic polymer systems [217–219]. These materials provide controlled degradation, endothelial compatibility, and tunable bioactivity, making them highly suitable for next-generation stents, vascular grafts, and heart valve replacements [220–222]. Their utility stems from the ability to integrate precise crosslinking strategies that enable modification of stiffness, porosity, and degradation kinetics—key parameters for cardiovascular device performance.

Biopolymer-Coated Stents Reducing Thrombosis Risk

The use of crosslinked biopolymer coatings on cardiovascular stents addresses complications such as thrombosis, restenosis, and delayed endothelialization [220, 223]. Functional polymers including chitosan, hyaluronic acid, dextran sulfate, and PEG derivatives can be covalently crosslinked using photoinitiated or enzymatic reactions to form hemocompatible coatings [207, 224, 225].

These coatings act as reservoirs for localized delivery of bioactive molecules such as anticoagulants (e.g., heparin, hirudin), anti-inflammatory drugs (e.g., sirolimus, paclitaxel), and endothelial growth factors (e.g., VEGF, SDF-1 α) [226, 227]. By integrating these agents into the crosslinked matrix, sustained release can be achieved over therapeutically relevant timescales. Additionally, functionalization with adhesion peptides (e.g., RGD motifs) facilitates rapid endothelialization, reducing the risk of in-stent thrombosis [228, 229].

Advanced strategies involve click chemistry-based modular coatings that allow spatial control over functional group distribution, and stimuli-responsive matrices that adapt to local flow or inflammatory signals. Bioresorbable stents with layered, crosslinked biopolymer coatings are under investigation for transient mechanical support followed by complete resorption, minimizing long-term foreign material burden [230, 231].

Crosslinked Vascular Grafts Mimicking Native Blood Vessels

The development of small-diameter vascular grafts (<6 mm) remains a significant challenge due to high failure rates caused by thrombosis, infection, and intimal hyperplasia. Crosslinked biopolymer-based grafts offer improved patency and remodeling by providing bioinspired compliance, hemodynamic compatibility, and resistance to aneurysmal dilation [232–234].

Materials such as decellularized ECM, collagen, elastin, silk fibroin, and polycaprolactone (PCL) are chemically or enzymatically crosslinked to enhance mechanical stability and reduce enzymatic degradation *in vivo*. The integration of nitric oxide (NO)-releasing moieties and endothelial progenitor cell-attracting ligands enhances hemocompatibility and accelerates *in situ* endothelialization [178, 232].

Advanced manufacturing techniques such as electrospinning enable the fabrication of multilayered, gradient-structured grafts that replicate the anisotropy and compliance of native vessels [235]. Hybrid constructs incorporating conductive polymers or shape-memory alloys with crosslinked matrices enable real-time functional tuning under physiological conditions.

Heart Valve Replacements with Prolonged Durability

Biopolymer-based scaffolds are increasingly used in the engineering of heart valves to overcome the limitations of mechanical and glutaraldehyde-fixed bioprosthetic valves. Traditional crosslinkers such as glutaraldehyde, while effective at stabilizing tissue, lead to cytotoxicity and calcification. Alternative crosslinkers like genipin, EDC/NHS, and poly(ethylene glycol) diglycidyl ether (PEGDGE) offer reduced immunogenicity and improved elasticity while preserving structural fidelity [235, 236].

Tissue-engineered heart valves composed of crosslinked collagen, fibrin, or decellularized pericardial matrices can be seeded with autologous stem cells or endothelial cells to form living, remodeling-capable valves. These constructs are being developed for transcatheter valve replacement (TAVR) and pediatric congenital valve repair, where long-term growth and adaptability are critical [237–239].

Recent innovations include microfabricated valves with nanostructured surface modifications that resist calcification and thrombosis, as well as dynamically crosslinked hydrogels that adjust mechanical behavior under hemodynamic loads. Research is also exploring composite valves with crosslinked hydrogel cores and fiber-reinforced exteriors to emulate the multi-layered architecture of native valves [240].

Crosslinked biopolymers represent a transformative approach in cardiovascular device engineering, offering biofunctionality, structural adaptability, and integration potential with host tissue. Their tunable crosslinking chemistries enable the design of devices that closely mimic the mechanical and biochemical milieu of the cardiovascular system. Future directions include the development of 4D biofabricated cardiovascular constructs, responsive coatings that react to biological cues, and fully resorbable, cell-instructive scaffolds that eliminate the need for permanent implants.

8 Challenges and Future Perspectives

8.1 *Biocompatibility and Cytotoxicity Issues*

While crosslinked biopolymers hold significant promise in biomedical applications, their clinical translation is often impeded by concerns related to biocompatibility and cytotoxicity. One of the primary limitations arises from the inherent toxicity and reactivity of traditional crosslinking agents such as glutaraldehyde and formaldehyde [122, 241]. These aldehyde-based reagents, although effective in forming stable covalent linkages, can lead to persistent aldehyde residues within the polymer matrix. These residues are known to provoke inflammatory responses, cellular apoptosis, and oxidative stress, particularly when implanted in vivo [242].

To mitigate these risks, alternative crosslinking strategies with improved toxicological profiles are under active investigation. Natural crosslinkers such as genipin,

derived from *Gardenia jasminoides*, and enzymatic approaches utilizing transglutaminase or tyrosinase enable crosslink formation under physiological conditions while significantly reducing residual toxicity. Furthermore, photochemical crosslinking systems employing visible-light-sensitive initiators such as riboflavin or lithium phenyl-2,4,6-trimethylbenzoylphosphinate (LAP) offer spatial and temporal control with minimized cytotoxic side effects [127, 243, 244].

Immunogenicity represents another critical concern, especially when crosslinking leads to structural alteration of native proteins or when synthetic reagents elicit undesired immune recognition. Residual chemical groups, unintended epitope presentation, and degradation byproducts can activate innate and adaptive immune responses, potentially leading to chronic inflammation or foreign body reactions. Hence, comprehensive immunotoxicological profiling—including cytokine release assays, complement activation studies, and macrophage polarization analysis—is essential during preclinical evaluation [245, 246].

Emerging research focuses on the development of non-fouling, immuno-evasive materials by integrating zwitterionic motifs, PEGylation, or biomimetic surface modifications into crosslinked networks [247, 248]. These approaches aim to suppress opsonization and immune cell recruitment by minimizing protein adsorption and masking immunogenic domains. Simultaneously, high-resolution analytical techniques such as Fourier-transform infrared spectroscopy (FTIR), nuclear magnetic resonance (NMR), and mass spectrometry are being employed to monitor crosslinking kinetics and detect residual reactants with high sensitivity [249–251].

In parallel, efforts to develop “self-eliminating” or bio-orthogonal crosslinkers—agents that undergo complete reaction and degrade into inert, non-toxic byproducts—represent a frontier in crosslinking chemistry [252, 253]. These innovations, combined with scalable purification technologies such as tangential flow filtration or affinity chromatography, are poised to enhance the safety profile of crosslinked biopolymer systems.

Addressing these biocompatibility and cytotoxicity challenges is pivotal for regulatory compliance, long-term in vivo performance, and clinical adoption of crosslinked biomaterials. Future advancements will likely be driven by interdisciplinary collaboration across material science, immunology, and biomedical engineering to achieve truly safe, functional, and patient-specific therapeutic platforms.

8.2 Regulatory and Commercialization Challenges

The translation of crosslinked biopolymer systems from research settings to clinical and commercial applications is often impeded by stringent regulatory frameworks and the absence of standardized manufacturing protocols. Regulatory bodies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) impose rigorous requirements concerning safety, efficacy, and quality control for all novel biomaterials intended for medical use [254, 255].

A major regulatory barrier lies in the classification of crosslinked biomaterials, which may fall into drug, device, or combination product categories depending on their intended use, degradation profile, and mode of action. This ambiguity complicates regulatory pathways and can result in prolonged review timelines and increased development costs [256–258]. Moreover, novel crosslinking agents—particularly those not previously approved for clinical use—must undergo exhaustive toxicological and pharmacokinetic evaluations, including ISO 10993 biocompatibility testing, to demonstrate safety [256, 259].

From a commercialization perspective, standardization remains a persistent challenge. Crosslinking processes are highly sensitive to parameters such as pH, temperature, reaction time, and polymer concentration [260]. Variability in these conditions can lead to batch-to-batch inconsistencies in mechanical strength, degradation rates, and bioactivity. This variability poses significant hurdles in scaling up from laboratory to industrial production, where Good Manufacturing Practice (GMP) compliance requires rigorous process control and validation [261, 262].

Efforts to address these challenges include the development of standardized protocols for crosslinking characterization—such as degree of crosslinking quantification, crosslink density measurements, and thermal/mechanical performance benchmarks [263]. In addition, quality-by-design (QbD) approaches and real-time process analytical technologies (PAT) are being integrated into manufacturing pipelines to ensure reproducibility and regulatory compliance [264].

Intellectual property (IP) protection is another key factor influencing commercialization. The novelty and proprietary nature of crosslinking chemistries must be well-documented through patent filings, which are often complex due to overlapping claims and broad classifications. Moreover, navigating freedom-to-operate analyses and licensing agreements can be resource-intensive, especially for academic spin-outs and early-stage companies [265].

Collaboration between academic institutions, industry stakeholders, and regulatory agencies is essential to establish clear guidelines, facilitate early dialogue on regulatory strategy, and accelerate the translation of safe and effective crosslinked biopolymer products to the market. Looking forward, the emergence of regulatory science tools, including predictive modeling, in silico simulations, and adaptive trial designs, will further streamline the approval and commercialization process for advanced biomaterials.

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Chapter 8

Biopolymers in Gene Delivery: Challenges and Opportunities

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Dharmanka Bandyopadhyay, Alok Shiomurti Tripathi,
and Sambit Kumar Parida**

Abstract Gene-based therapies are a novel approach to treating a wide range of diseases that are now incurable. However, gene therapies biological applications have been severely limited by their delicate nature. Thus, for gene-based treatments, the development of gene-delivery vectors is key. Gene delivery has been accomplished through the development and application of numerous gene-delivery vectors. They can generally be divided into vectors that are viral and those that are not. Non-viral vectors have emerged in recent years, garnering a lot of attention from researchers due to safety concerns with viral vectors. Among these polymeric, non-viral vectors have been favored because of their low immunogenicity, simplicity in manufacturing, regulated chemical makeup, and great chemical adaptability, making them the perfect substitute for viral vectors. With their favorable biocompatibility and biosafety, biodegradable polymers, in particular, have been seen as having a lot of promise for use in therapeutic settings. The purpose of this review is to provide the latest advancements in biodegradable polymers for gene delivery applications, with a focus on their capability for gene transfer, chemical structure design, and other biological functions. Accordingly, we identify and classify biodegradable polymers first, then go on to explain the mechanisms of breakdown associated with each. We will introduce and analyze the various biodegradable polymer types that arise from natural and manmade polymers, as well as their potential uses in gene transfer. Lastly, an outlook for the future of biodegradable polymer vector development will be provided.

Keywords Biopolymer · Gene delivery · Natural · Biodegradable and therapy

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Abbreviations

DNA	Deoxyribonucleic Acid
RNA	Ribonucleic Acid
CPs	Cationic Polymers
PEI	Polyethylenimine
PLL	Poly-L-lysine
PDMAEMA	Poly(2-N-(dimethylaminoethyl) methacrylate)
PLA	Poly(lactic Acid)
PGA	Polyglycolic Acid
PLGA	Poly(lactic-co-glycolic acid)
PHA	Polyhydroxyalkanoates
PHB	Polyhydroxybutyrate
PBAE	Poly- β -amino esters
DOPE	Dioleoylphosphatidylethanolamine
DOPC	Dioleoylphosphatidylcholine
PEG	Polyethylene Glycol
ECM	Extracellular Matrix
BBB	Blood-Brain Barrier
ABC	ATP-Binding Cassette
EPR	Enhanced Permeability and Retention
NCs	Nanocarriers
siRNA	Small Interfering RNA
HA	Hyaluronic Acid
PAMAM	Poly(amidoamine)
MMP13	Matrix Metalloproteinase 13
DGL	Dendrigraft Poly-L-lysine
γ -PGA	Gamma-Polyglutamic Acid
CPPs	Cell-Penetrating Peptides
RISC	RNA-Induced Silencing Complex
DOSPA	2,3-Dioleyloxy-N-[2(sperminecarboxamido)ethyl]-N,N-dimethyl-lpropanaminium trifluoroacetate
DOGS	Di-octadecyl-amido-glycyl-spermine
DOTMAN	[1-(2,3-Dioleyloxy)propyl]-N,N,N-trimethylammonium chloride
DOTAP	1,2-Bis(oleoyloxy)-3-(trimethylammonio)propane
DC-Chol	3 β [N-(N',N'-dimethylaminoethane)-carbamoyl]cholesterol
D/P	DOTAP/pDNA Lipoplex
mRNA	Messenger RNA
pDNA	Plasmid DNA
DDS	Drug Delivery Systems
AAV	Adeno-Associated Virus
HSV-1	Herpes Simplex Virus Type 1
sgRNA	Single Guide RNA
FDA	Food and Drug Administration

RBC	Red blood cell
NLS	Nuclear Localization Signal

1 Introduction

A novel and effective treatment for both acquired and inherited illnesses, including cardiovascular disease, diabetes mellitus, neurological problems, genetic disorders, and cancer, is gene therapy [1, 2]. In gene therapy, therapeutic ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) gene molecules can silence mutant genes, change missing genes, and change faulty genes. As our understanding of the genes that cause sickness grows, Gene therapy has shown promise as a treatment option for a number of diseases that are currently incurable. However, gene therapy's usefulness has been severely limited by the delicate nature of therapeutic genes. By way of serum nuclease assault, for instance, naked therapeutic genes quickly lose their initial bioactivity. Furthermore, due to their hydrophilic nature, high molecular weight, and negatively charged nature, therapeutic genes have minimal cell uptake, very poor cellular membrane permeability, and limited stability throughout blood circulation [3]. Gene therapy still faces a variety of external or intracellular biological barriers in addition to the ones already described. These obstacles consist of rapid clearance, immunological reaction, lack of selectivity to specific cells and tissues, endosomal escape, and unpacking problems. Given the fact that they can deliver therapeutic genes into specific cells, unpack genes intracellularly, and guarantee that the genes carry out subsequent transfection processes, gene-delivery vectors are crucial to gene therapy in this regard.

In line with this, therapeutic genes can demonstrate their maximum transfection efficiency with the least amount of negative patient effects when appropriate gene delivery vectors are used [4]. Cationic polymers (CPs) are made from a variety of polymers based on the delivery mechanism described. As an illustration, traditional polymeric vectors for gene transport have been widely employed. This incorporates poly(2-N-(dimethylaminoethyl) methacrylate) (PDMAEMA), poly-ethylenimines (PEI), and poly(L-lysine) (PLL). Conductive polymers may demonstrate a diverse range of polymeric structures, such as linear, branched, hyper-branched, dendritic arrangements, or star-shaped, predicated on the careful formulation of their chemical architecture [5, 6]. Additionally, every chemical structure can offer unique health benefits to the resultant CPs. Despite the fact that many CP-based vectors have been created, cytotoxicity is the primary factor influencing their use in later clinical settings. Previous studies have shown that two important factors contributing to cytotoxicity are the positive charges and the size of CPs. In normal cells, CPs with a large molecular weight and non-degradable linkages may build up. This buildup may negatively impact normal cells' ability to move and perform metabolic processes, ultimately leading to severe cytotoxicity. Furthermore, the majority of the widely utilized CP-based vectors, including PDMAEMA, PEI, and PLL are made

up of amide bonds and non-degradable vinyl ($-C-C-$) that cannot be broken down into residues of minimal molecular mass in a physiological setting for additional body clearance. Because of their inability to degrade, these CPs generate substantial buildup in the human body, particularly after been administered several times. The degradability of CPs also has a significant impact on how their loaded genes unpack inside the targeted cells [7–9]. Consequently, non-biodegradable CPs struggle to demonstrate their maximum gene-delivery effectiveness due to their high toxicity, which further restricts their potential therapeutic applications. Alternatively, their low molecular equivalents can be used. Such CPs are able to be removed from the human body due to their low molecular weight. A reduction in CPs' molecular weight, however, would lessen their capacity to bind with therapeutic genes, which would impact the effectiveness of transfection into the intended cells. Additionally, lowering the molecular weight of CPs also decreases their colloidal stability in an environment containing serum [10]. However, when creating and utilizing Vectors for gene delivery based on CP, such a tradeoff is not ideal. Biodegradable polymers have been used as component materials to create CPs for applications involving gene delivery in order to get over the aforementioned difficulties. Thus, biodegradable CPs can facilitate gene delivery methods by minimizing their toxicity to targeted cells and tissues and their accumulation quantity in treated cells. Additionally, their biodegradability can be used as a useful instrument to release the therapeutic genes that are loaded into the treated cells' cytoplasm. Thus, the creation of biodegradable CPs is crucial for gene-delivery applications. An overview of biodegradable polymers will be provided at the outset of this review. Generally speaking, there are three types of biodegradable polymers: natural, synthetic, and bioresorbable. The breakdown of the integrated labile links or hydrolysis of the polymer backbone are key factors in their degradation in physiological settings [11]. Biodegradable CPs are guaranteed to be biosafe because the breakdown of polymer structures makes it possible for them to be removed from the body through an excretion pathway. As a result, the advancement and growth of the three biodegradable CP kinds listed above in gene-delivery applications will be examined. Additionally, a future outlook on the creation and creation of CP-based gene delivery vectors that are biodegradable and next generation will be discussed. Considerable progress has been made in the design and development of biopolymer-based delivery systems in recent years for a variety of uses, such as vaccine administration, gene editing, cancer treatment, and regenerative medicine. These developments have reduced the frequency of dose and minimized off-target effects, opening the door for more accurate and efficient therapies. Furthermore, the development of advanced technologies like 3D printing and nanotechnology has allowed for the creation of complex delivery systems based on biopolymers with customized characteristics, allowing for the exact control of drug release kinetics and spatial distribution. There is significant potential for enhancing therapeutic results and reducing negative effects with this degree of personalization [12–14]. Crucially, the development of multifunctional delivery platforms that can get past biological barriers and deliver medications to particular cellular targets has resulted from the convergence of biopolymer science with other fields like molecular biology, materials science, and bioengineering. This confluence gives promise for

illnesses that were previously thought to be incurable and has the potential to alter the landscape of treatment. Biopolymer-based systems for delivering drugs and genes play a bigger role as we deal with issues like drug resistance, customized medicine, and the need for safer and more efficient treatments [15].

Precision medicine is becoming more and more attainable thanks to the capacity to customize delivery methods to each patient's unique profile, genetic variants, and illness characteristics. Biopolymers have become a promising class of materials for more accurate and effective delivery of therapies in the constantly changing field of pharmaceutical research and development [16]. Some intriguing examples of current studies and advancements in the design, synthesis, and use of biopolymers for drug and gene delivery were presented in emphasizing their special benefits, which include low immunogenicity, biocompatibility, and biodegradability. Targeted distribution, sustained release, and improved therapeutic efficacy are just a few of the answers it shown how biocompatible and biodegradable polymers can address the problems with traditional drug and gene delivery system [17].

2 Classification of Biopolymers Used for Gene Delivery

Current trends in biodegradable aliphatic polymers include advancements in new design techniques and applications in the biomedical sector. Serving as non-viral vectors, these polymers demonstrate beneficial qualities such as ease of synthesis, cost-effectiveness, biodegradability, lack of immunogenicity, high tunability, and the capacity to encapsulate nucleic acid therapies via polyelectrolyte complexes. Various fabrication procedures applied include solvent displacement, solvent evaporation, emulsification–solvent diffusion, and monomer polymerization. The biopolymers utilized in drug delivery systems typically comprise3 dendrimers, polylactic acid (PLA), PEI, and chitosan (CS), each characterized by specific structural features, production processes, and properties. Biopolymers are usually viewed as being carbon neutrality. Biodegradable polymers, which are alternatively referred to as biopolymers, can be divided into natural and synthetic kinds. The origins of biopolymers may be attributed to both renewable and nonrenewable resources. Examples of biopolymers encompass carbohydrate polymers produced by microorganisms such as bacteria and fungus, including cellulose, starch, and alginate, in addition to animal protein-derived polymers such as wool, collagen, silk, gelatin, and chitin/chitosan. This study attempts to present a full overview of the biopolymer classification in gene delivery, classifying them according to their origin, chemical structure, ionic charge, and functional qualities related to their usage as gene carriers [18, 19].

Biopolymers have received considerable scholarly attention in various applications necessitating sustainable and biodegradable alternatives. The implementation of drug delivery systems aimed at augmenting the efficacy of bioactive compounds constitutes a crucial approach for therapeutic interventions, with notable advancements being observed in this domain. Synthetic, natural, and semi-synthetic polymers are frequently used in this context when developing drug delivery systems.

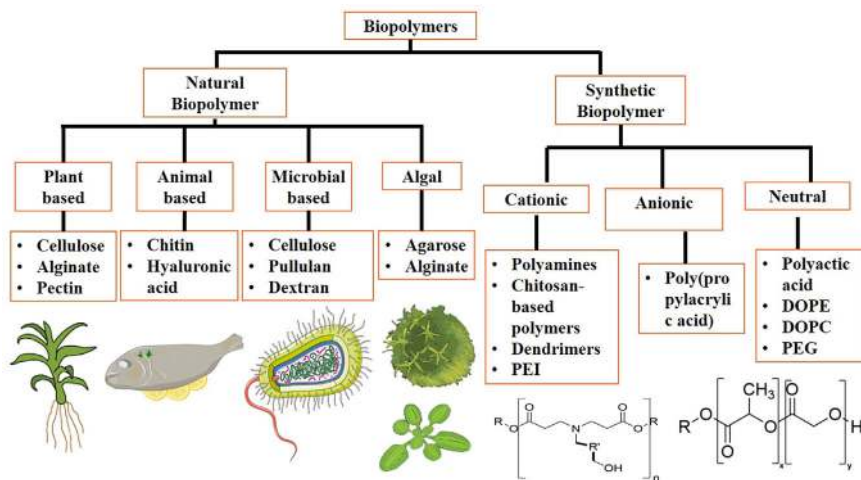


Fig. 1 Classification of biopolymers based on their nature. (Classification of biopolymers into natural and synthetic categories. Natural biopolymers are further divided into plant-based (e.g., cellulose, alginate, pectin), animal-based (e.g., chitin, hyaluronic acid), microbial-based (e.g., cellulose, pullulan, dextran), and algal-based (e.g., agarose, alginate). Synthetic biopolymers are categorized based on their charge properties into cationic (e.g., polyamines, chitosan-based polymers, dendrimers, PEI), anionic (e.g., poly(propylacrylic acid)), and neutral (e.g., polylactic acid, DOPE, DOPC, PEG). The diagram includes representative illustrations of sources and structural representations of selected biopolymers)

The source of these polymers allows for a systematic classification into two main groups [20, 21]. Plant-based biopolymers, including cellulose, hemicellulose, and starch, have long been prized for their accessibility and adaptability. Polylactic acid (PLA), polyhydroxyalkanoates (PHA), and polyhydroxybutyrate (PHB), and bacterial cellulose are examples of biopolymers that come from microorganisms and are becoming more and more popular because of their biodegradability and adaptability. The development and use of biopolymers presents a workable way to address the problems caused by synthetic polymers [22] (Fig. 1).

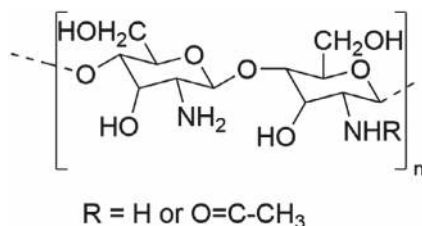
2.1 Natural Biopolymers for Gene Delivery

Natural polymers, synthesized from organic entities including algae, microorganisms, flora, or fauna, have been extensively utilized for several decades in the field of biomedicine, scaffolds for drug delivery systems, tissue regeneration, and medical imaging [23]. The category of natural polymers encompasses polysaccharides, proteins, and polyesters that are sourced from both the plant and animal kingdoms. A significant number of these polymers are constituents of our nutrition and have been applied in an array of human endeavors. These polymers are identified by



the biological surroundings and are subsequently guided towards catabolic processes. Naturally occurring polymers display similarities to the elements of the extracellular matrix (ECM), hence aiding evasion of persistent toxicity and immunological responses, which are often associated with synthetic polymers [24].

2.1.1 Chitosan

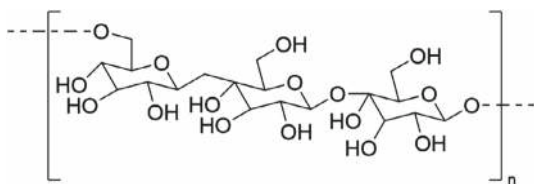


Chitosan, derived from the exoskeletal structures of marine crustaceans like crabs and shrimps offering the advantageous characteristics of biodegradability and biocompatibility, attributes that are highly sought after in relation to medication delivery systems. A polymer made up of successively ordered units of N-acetyl-d-glucosamine and D-glucosamine is called chitosan. Every chitosan subunit has a main amine group and two hydroxyl groups after the deacetylation process. These groups are easily chemically changed according to particular uses. Chitosan becomes cationic and soluble when its amine groups are protonated to create ammonia at pH values below 6.5. Furthermore, chitosan's solubility is strongly impacted by its molecular weight, degree of deacetylation and pH [25, 26]. Neurological disorders impact over one billion individuals worldwide, yet there remains an inadequate supply of effective pharmacological interventions. A significant proportion of novel therapeutic agents experience failure due to suboptimal transport across the blood–brain barrier (BBB) and pronounced efflux mediated by ATP-binding cassette transporters, resulting in adverse effects including diabetes, seizures, and toxicity. Current research is focused on “Enhanced permeability and retention” (EPR) nanocarriers for facilitating transport across the BBB in the treatment of the central nervous system associated with diseases. Chitosan, a biocompatible polysaccharide, serves as a proficient transfection agent, exhibiting biodegradability in vivo and the capacity to form complexes with negatively charged DNA. Chitosan nanoparticles have demonstrated remarkable in vitro transfection efficacy across several cell lines such as MSCs, HEK293 MG63, and A549. Although data pertaining to malignant brain cells remains limited. The lack of effective transfection agents capable of traversing the BBB underscores a critical imperative for the advancement of future gene delivery methodologies [27]. The presence of amino and hydroxyl groups in the chitosan backbone makes chemical modification to enhance its characteristics and efficacy. The quaternization of amino functional groups can be employed to facilitate the solubility of medium and low molecular weight chitosan in aqueous environments across



an extensive pH spectrum, while concurrently imparting a regulated cationic property [28]. These synthesized compounds illustrated greater water solubility compared to chitosan and displayed negligible cytotoxicity towards Hek293 kidney cell lines. The ovarian SKOV-2 and cell lines for breast cancer MCF-7 showed remarkable transfection efficiency with these resulting nanoparticles [29, 30]. Similar to PEI, O-methyl-free N,N,N-trimethylated chitosan showed strong gene suppression in H1299 human lung cancer cells that produced firefly luciferase when combined with siRNA. This suggests that chitosan derivatives could be involved in siRNA delivery [31]. Through the use of a pancreatic cancer xenograft model, it was discovered that folic acid conjugated nanoparticles which greatly enhances siRNA delivery targeting several genes. Furthermore, they prevented peritoneal spread and retroperitoneal invasion much more than other nanoparticle formulations [32].

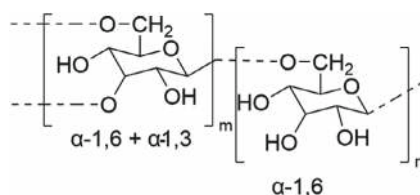
2.1.2 Pullulan



A water-soluble polysaccharide termed as pullulan is characterized by the presence of α -1,6-glucopyranose and α -1,4-glucopyranose monomeric units [33, 34]. Its properties include non-toxicity, non-immunogenicity, non-carcinogenicity, and non-mutagenicity. The derivatization of pullulan with cationic entities, such as spermine, has the potential to yield positively charged nanoparticles exhibiting remarkable binding affinity for DNA and enhanced efficacy in gene transfection [35]. Priya et al. successfully synthesized cationic pullulan through the conjugation of this polysaccharide with protamine [36]. This resultant polymer demonstrated the capability to inhibit DNA degradation and exhibited significant hemocompatibility, alongside an enhancement in cellular viability. In order to deliver a genetic construct and a chemotherapeutic drug simultaneously, a recent study described creating a redox-responsive platform by mixing a pullulan derivative that is charge-reversible (CAPL) with disulfide-containing poly(beta-amino ester) (PBAE) [37]. This chemical entity was able to condense DNA and facilitate the delivery of dye-labeled plasmid DNA within human hepatoma HepG2 cells. Furthermore, the conjugation of pullulan was found to augment the gene delivery efficiency of PAMAM dendrimer within the HepG2 cell line [38].

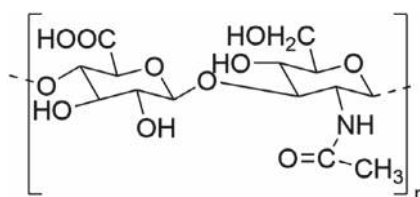


2.1.3 Dextran



Dextran represents an additional carbohydrate polymer that finds application in biomedicine and gene transfer methodologies. A modest amount of 1,3-branching is seen in this polymer, which is primarily composed of α -1,6-linked glucopyranose units [39, 40]. To facilitate siRNA distribution, cationic methacrylate monomers can be used to derivatize cationic, biodegradable dextran hydrogel nanoparticles [41]. Moreover, polyelectrolyte complexes of polymers with a positive charge, like poly-L-arginine, can be formed by negatively charged dextran sulfate for the transport of siRNA [42, 43]. When dextran-grafted branching PEI is used, it has been shown to greatly increase the PEI compounds' stability with DNA when bovine serum albumin (BSA) is present [44]. By using the MTT assay, it was discovered that dextran-PEI conjugates had a reduced toxicity profile than their unmodified PEI versions [45]. In comparison to PAA-DNA nanoparticles, nanoparticles produced by complexing polyallylamine (PAA)-dextran conjugates with DNA demonstrated a higher transfection efficiency. The chitosan-dextran conjugates on the JU77 and ONE58 cell lines demonstrated remarkable frizzled-related protein 4 (SFRP4) transfection effectiveness [46]. The luciferase expression of peptide-grafted dextran containing histidine (H) was 6–8 times higher than that of 25 kDa branching PEI [47].

2.1.4 Hyaluronic Acid



Hyaluronic acid (HA) is an anionic polymer with a wide range of biological uses, such as gene delivery systems and therapeutic interventions. It is made up of N-acetyl-D-glucosamine and D-glucuronic acid [48]. Since the CD44 receptor is often overexpressed on the membranes of different tumor cell types, HA interacts with it to make it an ideal carrier for the targeted delivery of drugs and genetic materials to neoplastic cells. HA and polycations, like polyarginine, can interact electrostatically to produce nanogels [49]. The siRNA and HA interact through van der Waals forces,



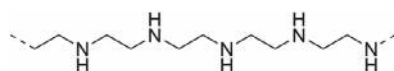
which has been used to effectively silence genes in human mesenchymal stromal cells and a CD44-positive human osteosarcoma cell line (MG63) [50]. Formulations of nanoparticles created by complexing HA conjugated with polyethylene glycol (HA-PEG) and HA-polyethylenimine (HA-PEI) have shown encouraging results in gene transfection and expression in human lung cancer cell lines A549 and HeLa with negligible cytotoxicity [51, 52]. In a mouse model of hepatic fibrosis, HA was complexed with PEI and used to transport the MMP13 gene with impressive effects [53]. They transfected HEK293 kidney cells with NIH2T3 fibroblasts in vitro using HA-based polyelectrolyte multilayers with lipoplexes carrying plasmid DNA and Glyc-CHI [54]. To give colorectal cancer cells an anti-KRAS siRNA, ternary nanocomplexes were created using HA conjugates with chitosan and polyhexamethylene biguanide. Using the interaction between HA and CD44, the method preferentially targeted neoplastic cells that were CD44-positive [51]. Moreover, multilayers of HA/PEI were developed to support gene silencing and make siRNA transport easier [55].

2.2 *Synthetic Polymers for Gene Delivery*

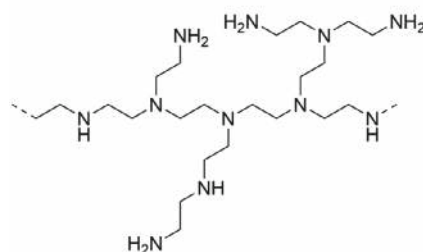
Cationic compounds currently being investigated for their efficacy in gene transport encompass a diverse array of organic cations, such as polymers and cationic lipids containing polyamines, PEI, dendrimers, and chitosan-based polymers [56]. These polymers are crucial in the gene transfer process as they form complexes with DNA, resulting in the development of small, nanoscale polyplexes [57]. The densely packed inner core of the polyplex achieves charge neutralization, rendering it resistant to degradation by nucleases; consequently, the encapsulated nucleic acids remain stable and intact until effective uptake by target cells occurs [58]. Despite the non-biodegradable nature of PEI, which is a polymer in itself, it has garnered attention in gene transport studies due to its remarkable transfection efficiency. To mitigate its cytotoxic effects and enhance its biocompatibility, numerous modifications aimed at rendering it biodegradable have been explored by researchers, and although intrinsically non-biodegradable, its polymeric nature positions it as a viable option for gene transfer applications [59].



2.2.1 Polyethyleneimine and Its Biodegradable Derivatives



Linear polyethyleneimine

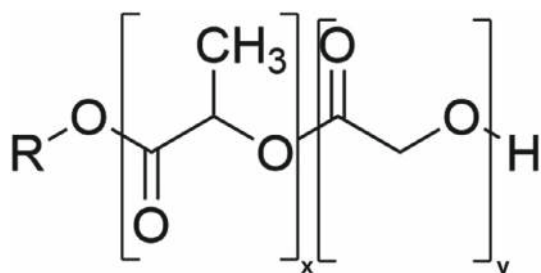


Branched polyethyleneimine

Among the extensive variety of cationic polymers characterized by amine functionalities in their polymeric architectures, Polyethylenimine (PEI) has become one of the most rigorously investigated agents for gene transfection. Its importance in this area dates back to 1995, when Boussif et al. conducted a groundbreaking study in which they discovered that it was an effective gene transfection agent. In both vivo and in vitro studies, PEI has demonstrated significant transfection success in both its branched and linear structural configurations [60]. Molecular weight, target cell type, and the structural shape of the polymer (either linear or branched) are important parameters that affect how well PEI facilitates gene transfection. PEI can interact with and condense negatively charged DNA molecules because, in physiological settings, about 20% of its nitrogen atoms are protonated. This interaction not only shields the genetic material from lysosomal deterioration but moreover augments the expression of the transfected gene [61, 62]. Investigations employing fluorescently labeled PEI and DNA have revealed that DNA adheres to cellular surfaces and aggregate into clusters that are subsequently internalized via endocytosis. Moreover, experimental results indicate that subsequent to endocytosis, PEI—whether administered independently or in conjunction with DNA—can achieve nuclear localization in a structured manner. Notably, it has been observed that the nuclear delivery of DNA is markedly more efficient when utilizing a 22 kDa linear PEI in comparison to its branched alternative [63].

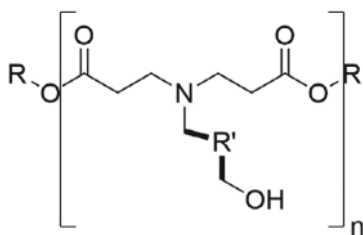


2.2.2 Poly Lactic-co-Glycolic Acid



Poly lactic-co-glycolic acid (PLGA) refers to a category of FDA-sanctioned biodegradable polymers that are recognized for their superior mechanical strength, remarkable biocompatibility, and widespread application as carriers for pharmaceuticals, proteins, and various macromolecules, including RNA, DNA, and peptides. The copolymer polyester PLGA, which is made of polylactic acid (PLA) and polyglycolic acid (PGA), is amongst the most well-characterized biomaterials for drug administration in terms of both functioning and design. PLA has asymmetric-carbon that can exist in two enantiomeric forms: D-lactic acid (PDLA) and L-lactic acid (PLLA). These enantiomers are typically described using conventional stereochemical nomenclature as the D and L configurations, or alternatively, as the R and S isomers, respectively. The term “PLGA” predominantly denotes L-lactic-co-glycolic acid, poly D, in which the both D- and L-lactic acid types can be found in a balanced ratio [64].

2.2.3 Poly- β -Aminoesters

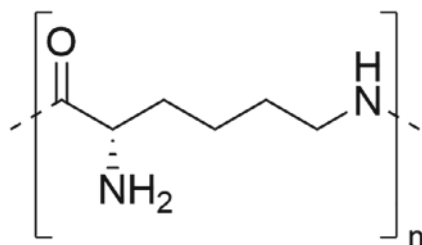


PBAE molecules engage with DNA with the use of electrostatic forces, which leads to the formation of nanoparticles (100–200 nm) characterized by their biodegradable and non-cytotoxic properties, exhibiting a half-life ranging from 1 to 7 h in aqueous environments [65–67]. Guerrero-Ca'zares et al. demonstrated the considerable effectiveness of transfection of PBAE-based nanoparticles within cells of glioblastoma in vitro and in a patient-derived orthotopic animal model [68, 69]. The enzyme-mediated lactone copolymerization using dialkyl diester and amino



diols resulted in the creation of polyamine (co-esters), which facilitated superior DNA transport in HEK293, U87-MG, and 9L cells, thereby enabling targeted TRAL gene delivery with minimal toxicity in tumor xenograft models [70]. Additionally, PBAE also synthesized nanoparticles in conjunction with minicircle DNA, thereby enhancing transgenic expression *in vivo*. Mastorakos et al. engineered resilient, mucus-penetrating PBAE-based DNA nanoparticles (PBAE-MPPs) aimed at treating respiratory diseases and lung cancer, achieving significant transgene expression in animal lung tissues over a duration exceeding four months while maintaining a high safety profile. Surface-modified PLGA/PBAE nanoparticles exhibited promising potential for pulmonary gene delivery and editing applications [71]. PEGylated PBAE nanoparticles demonstrated improved circulation longevity and effectively infiltrated brain tumors, thereby augmenting transgene expression and survival rates in orthotopic brain tumor models [72]. Poly(amine-co-ester) terpolymers were created by Kauffman et al. using enzyme-catalyzed polymerization procedures to deliver plasmid DNA, miRNA, and siRNA. This allowed for a precise synthesis that depended on the particular cell type and nucleic acid properties [73]. In serum-containing medium, branched poly(esteramine) quadpolymers (BEAQs), which were created by Michael addition, were adjusted for improved transfection effectiveness [74, 75]. Reducible branched ester-amine quadpolymers (rBEAQs), which are currently being developed for non-viral CRISPR gene delivery, facilitate the co-delivery of Cas9 DNA and siRNA editing applications [76].

2.2.4 Poly-L-Lysine (PLL)



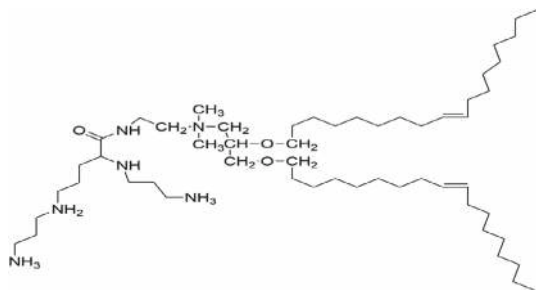
Poly-L-lysine (PLL) and its lower molecular weight derivatives, known as oligolysines, have been subjected to extensive investigation regarding their ability to condense deoxyribonucleic acid (DNA) into nanoscale particles for the purpose of gene delivery [77]. Nayvelt et al. investigated the PLL-mediated compaction of DNA, which resulted in the formation of various geometrical structures including spheroids, toroids, cubes, and rods; conversely, Korolev et al. documented interactions with plasmid DNA that were both salt-dependent and salt-independent [76, 78].



The modification of polyethyleneimine (PEI) with PLL has demonstrated an enhancement in transfection efficiency within HeLa cells while concurrently reducing cytotoxicity [79, 80]. Malik et al. elucidated that PLL-modified PEI facilitated the application and implementation of suicide gene therapy in the context of glioblastoma [81, 82]. Furthermore, copolymers derived from PLL are currently being looked into for their possible potential to improve gene delivery mechanisms [83]. In addition, other cationic peptides, particularly cell-penetrating peptides (CPPs), have shown promise as biodegradable vehicles for gene delivery [1]. CPPs, which are modeled after the HIV-1 Tat protein (GRKKRRQRRRPQ) and the penetrating peptide (RQIKIWFQNRRMKWKK), enhance the transport of siRNA and DNA, with transport efficiency being influenced by the length of the peptide sequence and the positioning of arginine residues. The development of tumor-targeting peptides, including Lyp-1 and RGD, has made it possible for DNA cargo to be directly transferred to neoplastic tissues by binding to epithelial cells [2].

2.3 Multivalent Cationic Lipids

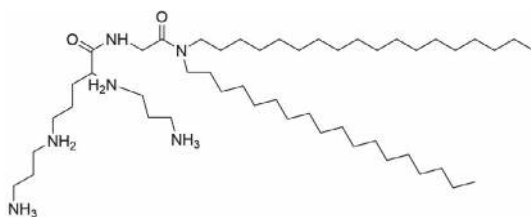
2.3.1 DOSPA



DOSPA (2,3-di-oleoyloxy-N-[2(sperminecarboxamido)ethyl]-N,N-dimethylpropanaminium trifluoroacetate) is a modified version of DOTMA, by creating hydrogen bonds with DNA, the spermine group improves the efficiency of DNA packing, fortifying the connection and stabilizing the lipoplex structure [84]. By attaching itself to negatively charged DNA and creating lipoplexes, which are then internalized by cells through endocytosis, DOSPA makes gene delivery easier. DOSPA increases the effectiveness of gene transfection while preserving biocompatibility because of its potent DNA condensation capacity [85].

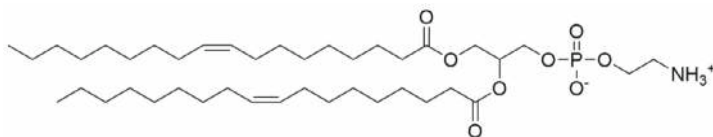


2.3.2 DOGS



DOGS (di-octadecyl-amido-glycyl-spermine) shares structural similarities with DOSPA but features saturated 18-carbon alkyl chains attached to a multivalent spermine through a peptide bond. In order to effectively bind and condense DNA and create stable lipoplexes, this big head group is essential[86]. Long alkyl chains enhance cellular absorption via enhancing membrane contact. Like DOSPA, DOGS ensures compactness and protection by establishing hydrogen bonds with DNA to facilitate gene transfection. Because the spermine group improves electrostatic contact with DNA, DOGS is a powerful carrier for applications involving non-viral gene delivery [87].

2.3.3 Neutral Lipids



DOPE

Neutral lipids such as dioleoylphosphatidylethanolamine (DOPE) and dioleoylphosphatidylcholine (DOPC) are widely utilized in combination with cationic polymers to enhance gene transfection efficiency. These lipids play an important role in stabilizing lipoplexes and facilitating the intracellular delivery of genetic material. DOPE, in particular, undergoes a conformational transition at acidic pH, adopting an inverted hexagonal phase structure. This unique structural change aids in condensing DNA through electrostatic interactions, thus raising the stability of the complete delivery system [88].

Endocytosis internalizes the lipoplex (lipid-DNA complex) during gene transfection, trapping it inside endosomal vesicles. By encouraging membrane fusion and destabilization, which permits the DNA's discharge into the cytoplasm, DOPE improves endosomal escape. This process is essential for maintaining effective gene expression and stopping DNA deterioration inside lysosomes. Additionally, to improve lipoplex stability, cellular uptake, and transfection effectiveness,



cationic polymers like DC-Chol, DOTAP, and many other cholesterol derivatives are frequently added to DOPE. By enhancing DNA protection, cellular entrance, and intracellular trafficking, neutral lipids and cationic carriers work in concert to increase gene delivery and therapeutic results [89].

2.3.4 Poly(ethylene) Glycol (PEG)

Polyethylene glycol (PEG) is a polyether derived from ethylene oxide with the chemical formula ($C_{2n}H_{4n+2}O_{n+1}$). Its physical attributes change according to its molecular weight and chain length, but its chemical properties stay the same. PEG comes in a variety of structural shapes, each with specific uses, such as comb, star, and branched PEG. PEG is extensively utilized in drug delivery systems because of its renal excretion, non-toxicity, and biocompatibility [90].

PEG is used extensively in the process of PEGylation, which modifies the surface of liposomes. This alteration gives liposomes stealth qualities, which enable them to avoid the mononuclear phagocyte system's (MPS) quick clearance and extend their bloodstream circulation time [91]. PEGylated liposomes show increased gene transfection efficiency, enhanced bioavailability, and decreased macrophage absorption. PEG's hydrophilia prevents early degradation and improves stability by forming a steric barrier around the liposomal surface. PEG is a crucial part of contemporary gene therapy and medication delivery systems since it also enables targeted gene delivery, guaranteeing effective cellular uptake and regulated release of genetic material [92].

3 Mechanism of Biopolymers for Gene Delivery

Biopolymers are flexible transporters of genetic materials like DNA, siRNA, and RNA, they are essential for gene therapy because they shield the materials until they reach their target cells. Conventional gene delivery raises safety concerns; biopolymer-based nanoparticles help treat cancer and genetic diseases. Effective gene release through electrostatic interactions and biocompatibility and biodegradability are desirable properties of ideal polymeric vectors. Their molecular weight, content, and structure are among their physicochemical characteristics that affect toxicity and the effectiveness of gene transfer [93]. Additionally, factors like particle size, surface charge, and morphology play a crucial role in the successful delivery of hereditary material. Biopolymers also enable targeted and controlled release, enhancing the results of therapy minimizing adverse effects. Ongoing research aims to enhance biopolymer safety and functionality by refining nanoparticle designs and formulations, establishing them as a potential tool for advancing gene therapy [94].



3.1 Mechanistic Pathway Involved During the Non-viral Gene Delivery of Biopolymers

The processes of chemical alteration, large-scale manufacture, and non-viral gene delivery are very simple. Importantly, the gene size to be transmitted is not a constraint on non-viral vector systems [95, 96]. There are two types of non-viral gene delivery vectors: chemical systems, such as polymeric materials, and physical techniques, as needle injection, microinjection, magnetoporation, sonoporation, electroporation, and gene guns. Due to their cationic nature, the majority of chemical systems can create positively charged complexes by electrostatically binding with negatively charged DNA [97]. These complexes enter cells by attaching itself to cellular membranes that are negatively charged. To deliver the transgene to the cytoplasm (for mRNA) or nucleus (for DNA), they must avoid lysosomal and endosomal destruction once they are inside [98]. Biocompatible polymers are used in polymeric gene delivery systems to safeguard genetic material from degradation, improve cellular uptake, and encapsulate it mainly by electrostatic complexation (DNA or RNA). These systems offer lower immunogenicity, scalability, and design versatility. Significant attempt for over the last 20 years to develop cutting-edge instruments and materials for the transport of entering cells with nucleic acids [99]. Transfection reagents, which are often used, are cationic lipids and polymers because of their efficiency and user-friendliness. They help with intracellular transport by forming lipoplexes and polyplexes with anionic NAs [100]. Since mRNA technology provides a versatile platform for rapid development and customized treatments, it has revolutionized gene delivery [101]. It can instruct cells to produce certain proteins, which makes it an excellent treatment for a number of ailments, includes infection caused by viruses and genetic disorders. Recent advances in lipid-based nanoparticles and further delivery methods based on nanoparticles technologies have significantly improved mRNA stability, cellular absorption, and targeted delivery. The potential of mRNA in pandemic preparedness and personalized medicine has been shown by this, resulting in successful applications in vaccines and therapies. The ground-breaking impact of mRNA on gene therapy is demonstrated by ongoing research and development [102]. One of the most used techniques is liposomes are employed in order to introduce genes into cells and cationic lipid transfection. Preventing toxicity from damaging the body is the main objective of most gene therapy attempts that use liposomes to transfect foreign genes. Thus, transfection efficiency is affected by several factors, including the cell density, liposome-to-plasmid ratio, transfection duration, and serum content in the medium. Ongoing study is required to investigate the best transfection settings in order to increase transfection efficiency and safety [103]. Because polymer design, production, and optimization are complicated, the creation of gene delivery polymer systems has lagged behind that of lipid systems. Polymers frequently have toxicity and biocompatibility issues, necessitating significant changes to guarantee safety and effectiveness. Lipid systems, on the other hand, have the advantages of easier formulation procedures and well-established, tested technologies. Despite these obstacles, research is still being conducted to solve the



limitations of polymers and speed up their development. The capacity of polymer-based drug delivery systems (DDSs) to target tumor tissues and improve therapeutic efficacy has drawn a lot of attention [64]. By controlling drug release rates that target certain biological locations, polymer-based drug delivery systems (DDSs) improve safety, bioavailability, and efficacy. These technologies provide a safe and efficient way to get around the drawbacks of chemotherapy in the treatment of cancer using biodegradable, bio-absorbable polymers [104]. The micelle polyplex was covered having a layer of hydrophobicity between complexed pDNA cores and poly(ethylene glycol) shells to construct an efficient non-viral systemic gene vector. It was simple to complex pDNA with mixed block copolymers to produce the hydrophobic layer. With cationic polymers generating DNA complexes and enabling cellular distribution, polymeric systems demonstrate the ability to deliver genes non-virally. Because of their potential for gene delivery applications, these polymers have been thoroughly investigated [105]. Figure 2 depicts the underlying mechanistic approach for gene delivery involving biopolymers.

3.2 Mechanism of Various Biopolymers Utilized for Gene Delivery

3.2.1 Dendrimers

The ability to precisely manage their size and shape is essential for gene delivery applications, and dendrimers are a special class of monodisperse macromolecules with a completely branching structure. In order to aid in gene transfection and targeted distribution, they can create stable complexes with genetic materials like DNA, which are frequently contained in water-soluble polymers [106]. The incorporation of ester groups into the backbone of biodegradable dendrimers allows them to safely break down in physiological settings, lowering toxicity and improving biocompatibility. Both of their synthesis processes—convergent and divergent—allow for customized gene delivery features [107]. Due to their large molecular weight, dendrimers preferentially accumulate in tumor tissues, making them promising candidates for targeted cancer gene therapy. Additionally, their cationic nature, particularly in poly(amido amine) (PAMAM) dendrimers, allows for strong electrostatic interactions with negatively charged DNA, ensuring stable complex formation necessary for effective gene transfer. With their unique structural properties, biodegradability, and targeting potential, dendrimers offer a versatile and efficient platform for safe and effective gene delivery in therapeutic applications [108, 109].

Dendrimers exist in various forms, each designed to leverage specific properties for biomedical applications. Amino acid-based dendrimers are developed using amino acid building blocks such as tryptophan, phenylalanine, and glycine, offering advantages like chirality, hydrophilicity, and biorecognition [110]. Amino acids can be attached to organic or peptide cores or grafted onto regular dendrimers to create

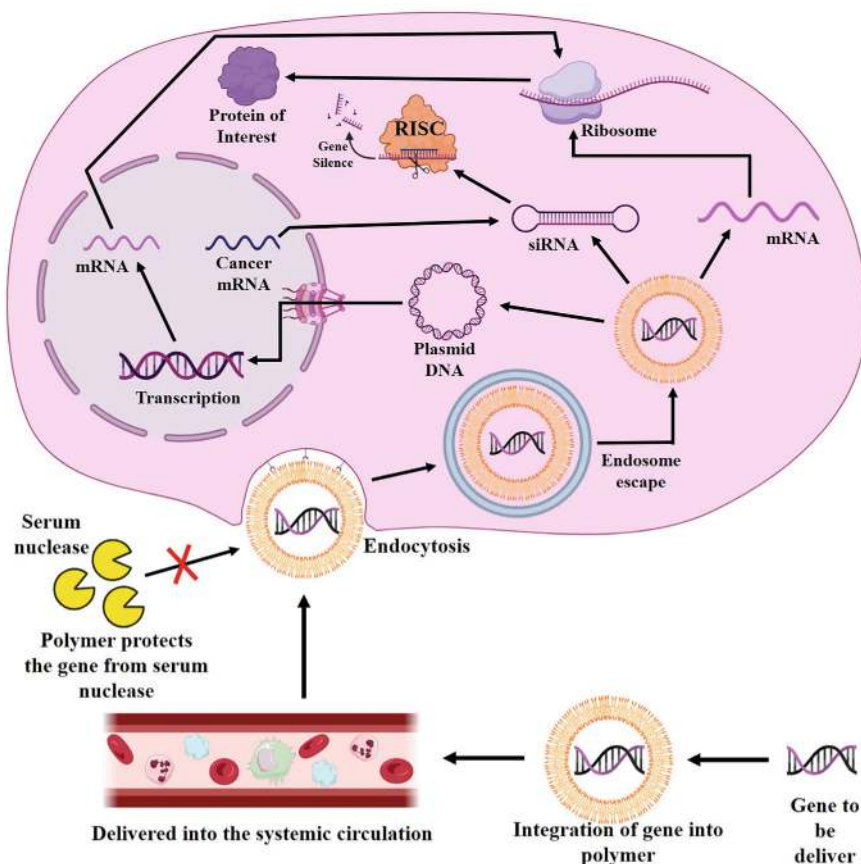


Fig. 2 Mechanism involved in gene delivery using biopolymers. (The figure illustrates a technology for delivering genes based on polymers that is intended for therapeutic use, specifically in the treatment of cancer. To prevent destruction by serum nucleases during systemic circulation, a gene of interest, such as plasmid DNA or siRNA, is first incorporated into a polymeric carrier. The gene-polymer complex stays stable in the bloodstream until it reaches the target cell, where endocytosis takes place and taken up by the cell inside an endosome. The complex breaks free from the endosome and releases the genetic material into the cytoplasm to guarantee efficient gene delivery. The genetic material then proceeds in one of two directions: (1) If plasmid DNA is the delivered cargo, it enters the nucleus, where it is translated by ribosomes into a functional protein of interest after undergoing transcription to produce messenger RNA (mRNA). (2) If the cargo is small interfering RNA (siRNA), it binds to the cytoplasmic RNA-induced silencing complex (RISC), which causes cancer-related mRNA to be specifically degraded, thereby suppressing the production of damaging genes. This polymer-mediated gene delivery system is a promising method for gene therapy in conditions like cancer because it improves stability, targeting, and therapeutic efficacy)

these dendrimers. Specialized dendrimers called glycodendromers interact with cell surface carbohydrate receptors to contribute to processes including cancer spread and lymphocyte activation. Glycosyl and mannopyranoside ligands are coupled to amine-terminated dendrimers to create them. Like amphiphilic polymer micelles, hydrophobic dendrimers have a hydrophilic surface and a hydrophobic core. This allows them to retain hydrophobic medicines within their branching architecture, improving their encapsulation and solubilization [111]. Dendrimeric copolymers come in two varieties: layer-block dendrimers, which have concentric spheres with unique chemical characteristics, and segment-block dendrimers, which are made up of segments with varying compositions. Every kind of dendrimer has special benefits for gene therapy, drug delivery, and biomedical research [112].

3.2.2 Chitosan

Chitosan is a cationic polysaccharide that serves as an effective nonviral gene delivery vector due to its low toxicity, biocompatibility, and ability to form stable polyplexes with nucleic acids. Its gene delivery strategy consists of several crucial phases. First, the phosphate groups of DNA or RNA combine with the chitosan to generate nanoparticles called polyplexes that contain the genetic information. After that, these nanoparticles are taken up by the cell membrane by endocytosis, which permits intracellular access. To prevent deterioration, the polyplexes must leave the endosomes once they are inside [113, 114]. Effective gene expression depends on this escape, which is frequently made possible by interactions with endosomal membranes or the proton sponge effect. Chitosan must release the genetic material into the cytoplasm after endosomal escape so that it can interact with other parts of the cell. While siRNA attaches itself to RISC, or gene expression is controlled by the RNA-induced silencing complex, plasmid DNA can then get to the nucleus for gene transcription. The N:P ratio, molecular weight, deacetylation level and are some of the variables that affect how well genes are delivered. Efficiency of transfection and cellular uptake are improved by optimizing these parameters. All things considered, chitosan is a promising substance for secure and successful uses of gene therapy because of its biodegradability, adaptability, and good gene protection properties [115].

3.2.3 Polyethylenimine

Polyethylenimine (PEI) is a cationic polymer extensively utilized in gene delivery because of its potent capacity for DNA condensation and efficient cellular uptake. PEI is a potent nonviral vector for gene therapy and DNA-based treatments because it facilitates nuclear entrance, endosomal escape, cellular absorption, DNA condensation, and DNA release [116]. Its mechanism goes through several important steps.

PEI first attaches itself to DNA and uses electrostatic interactions to create stable polyplexes. This encourages cellular absorption while shielding the genetic material from enzymatic destruction. Following their engagement with the cell that is negatively charged membrane, the positively charged polyplexes enable endocytosis, which allows entry into the cell. These complexes are retained in endosomes after internalization, where the proton sponge action of PEI causes membrane breakdown and osmotic swelling, allowing the DNA to escape into the cytoplasm prior to destruction [117].

For gene expression, the polyplexes must make it to the nucleus following endosomal escape. By causing transient structural alterations that allow DNA to enter the nucleus, PEI's contact with the nuclear membrane may aid in DNA transport. To start transcription, the DNA must be liberated from PEI once it is inside. This happens when PEI and nuclear components vie for DNA binding, which encourages decomplexation and gene expression [118].

3.2.4 Poly(α -L-lysine)

A cationic biopolymer that is frequently employed in gene transfer, poly(α -L-lysine) (PLL) can form stable complexes with DNA and promote cellular uptake. Several crucial processes are involved in its mechanism, all of which support effective gene transfer [119].

PLL forms polyplexes that shield DNA from enzymatic degradation and improve its cellular absorption by binding to plasmid DNA (pDNA) through electrostatic interactions. Structural changes, such as coupling PLL with hydrophobic regions like poly(L-Leu), can maximize the transfection effectiveness of PLL. Through improved internalization and lysosomal escape, these alterations enable the polyplexes to interface with cell membranes more successfully [120].

Endosomal trapping is a significant obstacle in gene transfer; nevertheless, PLL can be designed in order to enhance endosomal escape. The proton sponge effect is triggered when protonatable polyamine-containing polymers are added to PLL, increasing its buffering capability in the acidic endosomal environment. Osmotic swelling and membrane rupture are the results of this action, which permits the Genetic material being released into the cytoplasm [121].

The efficiency of cellular uptake is influenced by PLL's charge density and hydrophobicity. While a higher charge density enhances DNA condensation and stability, excessive charge can hinder DNA release. By optimizing these properties, PLL-based carriers can effectively transport genetic material into the nucleus, where it can be transcribed for gene expression. PLL-mediated gene delivery involves DNA complexation, cellular uptake, endosomal escape, and nuclear delivery, making it a promising nonviral gene vector [122].

3.2.5 Monovalent Cationic Lipids

N-[1-(2,3-dioleoyloxy)propyl] DOTMA Gene delivery frequently uses a cationic lipid called -N,N,N-trimethylammonium chloride. Four separate parts make up its structure: two linkage bonds, two hydrocarbon chains, a glycerol-based backbone, and a head quaternary ammonium group. The production of lipoplexes, which aid in the protection and entry of DNA into cells, is the result of the relationship between the head group that is positively charged and the negatively charged phosphate groups of DNA. Changes to DOTMA, like adding a hydroxyl in place of a methyl group, can increase interaction with the surrounding aqueous environment and boost protein expression. Furthermore, transfection efficacy is affected by the length of the aliphatic chain; shorter chains promote gene transfection, whilst longer chains may impede it [123].

DOTAP (1,2-bis(oleoyloxy)-3-(trimethylammonio) propane) shares similarities with DOTMA but differs primarily in its linkage bonds, where ester bonds replace ether bonds. This structural difference makes DOTAP more biodegradable and less cytotoxic, as the ester bonds undergo hydrolysis. DOTAP interacts with DNA to form lipoplexes, facilitating cellular uptake through endocytosis. However, because of its high density of positive charges, DOTAP alone is not ideal for gene delivery, as it can interfere with ion exchange. To enhance its gene delivery efficiency, DOTAP is often combined with helper lipids, which help improve stability and reduce cytotoxic effects [124, 125].

For gene delivery, DC-Chol (3 β [N-(N', N'-dimethylaminoethane)-carbamoyl] cholesterol) is a cationic lipid based on cholesterol. It has a dimethylethylenediamine group, which is essential for DNA binding, and a cholesterol moiety, which improves stability and biocompatibility. These components are joined by an ester bond, which hydrolyses the structure and encourages biodegradability. The efficacy of gene transfection is increased when DC-Chol and dioleoylphosphatidylethanolamine (DOPE) are mixed in a 1:1 ratio to generate persistent lipoplexes that inhibit aggregation and promote DNA dissociation inside cells [126] (Table 1).

4 Opportunities and Challenges in Biopolymer-Based Gene Delivery

A possible method for delivering gene biopolymers are used. Although the scientific community has studied the design of engineered nanoparticles which are made up of several molecules for particular responses as an alternative, work is still needed to enhance gene delivery. The design of hybrid nanoparticles must include many functionalities as cationic charge, condensation of nucleic acids, and targeted specificity. It takes a multidisciplinary team of scientists from several fields to create nonviral vectors for the inclusion of nucleic acids, assess biological efficacy, and ensure process development for commercial use.

Table 1 Application of biopolymeric systems and nanoparticles as gene carriers in different pathological conditions

Biopolymeric systems	Biomaterial	Applications and types of nanoparticles as gene carriers	References
Polysaccharides	Chitosan and derivatives	Treatment of osteoarthritis with graft-polyethylenimine/chitosan/DNA and chitosan nanoparticles	[127]
		Cancer treatment using chitosan nanoparticles containing silencing siRNA	[128, 129]
		pDNA delivery using chitosan/pentasodium tripolyphosphate nanoparticles	[128]
	Hyaluronic acid	DOTAP lipoplex is encapsulated in hyaluronic acid using Transfection of CD44-positive cells using PLGA-PEG copolymers	[130]
		For siRNA distribution, hyaluronic acid is coupled with hydrophobic amines, also known as fatty amines	[131]
	Cyclodextrin	PMCherry-C1 transfection into cancer cells using beta-cyclodextrin-chitosan nanoparticles	[132]
		The polyethylenimine, cyclodextrin, and tegafur as a delivery vehicle for genes and anticancer activity	[133]
	Alginate	Gene delivery via reverse microemulsion-produced Ca-alginate nanoparticles	[134]
		DNA nanoparticles made of alginate and CaCO ₃ are used to deliver genes and medications	[135]
Proteins and polypeptides	Albumin	Manufacturing of cationized albumin nanoparticles for use as gene delivery vehicles	[136]
		Using simple or complicated albumin nanoparticles to carry DNA or suicide genes to treat cancer	[137]
	Collagen	Calendula officinalis powder is delivered via gelatin/collagen stabilised with d-glucose for cancer treatment	[138]
	Casein	Preparation of chitosan-caseinate nanoparticle	[139]
		Manufacturing of magnetically sensitive casein nanoparticles	[140]

(continued)

Table 1 (continued)

Biopolymeric systems	Biomaterial	Applications and types of nanoparticles as gene carriers	References
	Gelatin	Delivery of siRNA via complex nanoparticles to silence the genes of cancer cells	[141]
	Recombinant proteins	Liposome-associated recombinant protein nanoparticles are used to introduce pDNA into cells	[142]

4.1 Opportunities in Biopolymers-Based Gene Delivery

Transferring gene expressions is achieved by delivering genes into cells in order to cure genetic abnormalities, which is known as gene delivery [143]. Polymers' chemical functional groups' variety, tunability, and capacity to build different physical topologies make them highly promising for the creation of gene delivery methods that are not viral. They will be designed to target particular cells or tissues, improve transport efficiency, decrease off-target effects, and modify immune responses while increasing gene transfer effectiveness, biocompatibility, and biodegradability. Despite recent developments, the scarcity of drug-related polymeric materials administration calls for the creation of new polymers for targeted and targeted delivery systems. Pharmaceutical companies also have to deal with rising clinical trial expenses and declining R&D pipeline rates of success for newly formed companies. The intricacy of selective targeting, particularly in highly toxic cancer medicines, clinical translation difficulties, high clinical trial costs, and declining success rates underscores the need for additional clinical research [144].

The cytotoxicity of polymers is one of the main obstacles to their use in gene transfer. Ongoing research, however, aims to create and synthesize novel polymers that are less harmful while preserving or improving their gene delivery effectiveness. To reduce cytotoxicity, techniques like the use of biodegradable polymers, regulated polymer architecture, and the incorporation of biocompatible components are being investigated. Regulatory bodies give priority to toxicity and therapeutic efficacy. Even if biodegradable materials are less dangerous, the need for high-throughput screening makes it difficult to create efficient RNA delivery methods. New delivery techniques that meet unmet therapeutic needs will result from increased non-viral RNA vector discovery efficiency [145]. In non-viral vectors in contrast to viral vectors are less immunotoxic, and future advancements could be facilitated by engineering better vector performance traits like trafficking, cytotoxicity, transfection, surface charge, and size [146].

Enhancing the effectiveness of non-viral systems' delivery is a crucial area of study. It is possible to design polymers that improve genetic material's nuclear localization, endosomal escape, and cellular absorption. The development of multifunctional delivery methods that get past different obstacles to effective gene transport,

the incorporation of targeted ligands, and the creation of smart polymers that react to particular cellular circumstances can all help achieve this [147].

Because they are biodegradable and biocompatible, natural polymers including chitosan, pullulan, and hyaluronic acid are desirable options for gene transfer. These polymers can be altered to improve their gene transport properties or employed in their natural state. Long-term toxicity and unfavorable immunological reactions may also be less likely when natural polymers are used.

Natural polymers can have their qualities for gene transfer enhanced by physical or chemical modification. Modifications could involve conjugating targeted moieties, adding stimuli-responsive regions, or adding functional groups that improve DNA binding. These changes can enhance the stability, effectiveness, and specificity of natural polymer-based gene delivery methods. Research on gene delivery is increasingly focusing on hybrid systems that combine the advantages of many materials. For example, polymer-coated nanoparticles can provide improved protection and regulated genetic material release. Likewise, the integration of synthetic and natural polymers can provide systems that capitalize on the benefits of both kinds of materials [148].

4.2 Challenges in Biopolymers in Gene Delivery

4.2.1 Effects Off-Target

Using biopolymers is a potential approach for applications involving gene delivery. An approach that has been thoroughly studied by the scientific community is the creation of engineered nanoparticles, which are made up of several molecules for particular reactions. Nevertheless, work is still required to enhance gene delivery. Among the characteristics to be designed are the many functions of hybrid nanoparticles, including cationic charge, nucleic acid condensation, and particular targeting. Designing nonviral vectors for nucleic acid inclusion, assessing biological efficiency, and ensuring process development for commercial objectives all require interdisciplinary competence with experts from several fields participating.

4.2.2 Maintaining Gene Stability Throughout Delivery

Because degradation may occur as a result of enzymatic action or physical uncertainties, it is imperative to ensure that genes stay intact and functioning throughout the delivery process. The *in vivo* stability of the mRNA, sgRNA, plasmid DNA, Cas9 protein, and external donor DNA is low due to their inherent biochemical characteristics. The Cas9 protein is susceptible to hydrolysis and destruction by proteases, and its blood's positive charge draws negatively charged substances, which speeds up clearance [149]. Delivery vectors must safeguard free DNA/RNA because nucleases in blood and interstitial fluid rapidly break it down. Proteins, RNA, and DNA

from exogenous plasmids are immunogenic and can elicit immune responses *in vivo*. Eliminating CpG patterns from plasmid DNA can decrease its immunogenicity [150].

4.2.3 Expanding Gene Cargo Capacity

The amount of genetic material that can be efficiently transported by polymeric materials varies depending on their size, shape, and surface characteristics. Different gene delivery techniques have different cargo capacities. For example, adeno-associated virus (AAV) vectors can normally hold up to 4.7 kb of genetic material, which can be expanded to 5.2 kb with modifications. Additional vehicles that offer unique benefits, including non-integrating capability include retroviruses, adenoviruses, Sendai viruses, HSV-1, transposon insertions, and episomal vectors [151].

4.2.4 Focusing on Particular Cells

To improve specificity and reduce off-target effects, polymeric carriers can be modified to target particular cell types using ligands or surface modifications. The negatively charged, hydrophobic cell membrane is difficult for DNA and RNA molecules to pass through because of their hydrophilia and negative charge. Both non-viral and viral vectors provide defense against degradation; however, after intravascular administration, they frequently do not deliver to specified cell types [152, 153].

4.2.5 Integrating Drug and Gene Delivery

In order to overcome drug resistance mechanisms in specific cells or provide synergistic therapeutic effects, polymeric systems can combine gene and drug delivery. Only a small number of the more than 2000 nanoformulations undergoing clinical trials reach the market because variations in production processes impact their efficacy and safety characteristics. Their potential for higher specificity and efficacy than conventional chemotherapeutics is highlighted by the EMA's regulatory recognition, underscoring the significance of exact nanomedicine development requirements [154].

4.2.6 Intracellular Trafficking and Localization and Cellular Uptake

Endocytosis processes, including macropinocytosis, caveolae-mediated, or clathrin-mediated, are commonly used by cells to absorb polymeric/gene particles, depending on their size and surface characteristics. Vector-supplied gene cargo typically leaves eukaryotic cells through the cytoplasm. For the cargo to exert its genetic influence, it must get all the way to the nucleus. Genetic material is transferred into the nucleus using a variety of techniques, depending on the type of vector. Viral vectors usually

travel via nuclear pore complexes by using nuclear localization signals (NLS) or by taking over the nuclear import apparatus of the host cell. To obtain nuclear entrance, non-viral vectors like lipid nanoparticles or polymer-based carriers may employ nuclear localization signals or endosomal escape mechanisms. When the payload enters the nucleus, it interacts with the genetic machinery of the cell, triggering the desired gene expression or modification [155].

This approach demonstrated improved cell motility, longer circulation in vivo, low cytotoxicity, and excellent transfection efficiency in ECs, as demonstrated by macrophage uptake and in vivo imaging. Gene delivery devices covered with RBC membranes have the potential to be both efficient and biocompatible in vivo. Examining these shell designs in detail will yield important information about how to improve therapeutic efficacy, increase the bioavailability of gene delivery systems, and optimize them [156].

4.2.7 Scale-Up Barriers and FDA Approval

It takes a lot of work and investigation to develop a gene-based system at the lab level. Replicating the same formulations at scale-up levels with comparable efficacy and submitting the data to FDA authorities for approval and commercialization presents a hurdle. The gene product and procedure must be proven safe and effective for the intended purpose in order to be approved. To regulate the quality of the final product, the process must be aseptically managed and adequately validated. After the formulation is developed, it takes between 8 and 12 years to complete the scale-up, clinical studies, and FDA marketing approval. Prior to human clinical trials, the created product must undergo preclinical and clinical testing for safety, toxicity, and efficacy on both healthy and diseased animals. One of the main obstacles to the development and marketing of these items is the unfounded safety concerns, which necessitate additional research and advancements before they can be offered safely [157, 158].

5 Perspectives and Conclusions

We began our review by providing a definition and classification of biodegradable polymers. Biodegradable polymers' important breakdown processes of biodegradable polymers have also been explained. Different biodegradable polymers, classified as natural and synthetic polymers, have been emphasized for their gene-delivery and chemical structure. The connections between these biodegradable polymers' structures and properties have also been arranged and examined.

Because it has a significant impact on the biocompatibility and biosafety of final biomedical products, biodegradability is now the most important material property influencing their clinical application. For gene-delivery vectors, biodegradability is especially important since gene-based treatments require recurrent injections. The

application of biodegradable polymers for gene transport and treatment has attracted a lot of interest from researchers.

Despite having good biodegradability, biocompatibility, and non-toxicity, there are still many obstacles to overcome before biodegradable polymer vectors can be developed from vivo to in vitro and eventually clinical trials. This is because several biological obstacles must be overcome for medical translation to be successful. The efficiency and stability of nucleic acids, as well as the creation of novel delivery systems, are only a couple of areas where non-viral gene therapy has advanced significantly in recent decades. So, scientists have been working on creating new and effective non-viral gene vectors. To improve delivery and reduce host cell toxicity, they carefully considered the polymeric vectors' chemical and physical makeup.

In comparison to viral gene vectors, non-viral gene vectors have demonstrated encouraging outcomes in safety, transfection, stability, and biocompatibility. Using macromolecules to get around the drawbacks of non-viral and viral vectors gene delivery has advanced significantly, putting safety, effectiveness, and tailored delivery first. Genetic cargo delivery has demonstrated potential with polymeric materials such as PLL, PEI, and PAMAM, while biocompatibility and specificity are improved by modifications like PLL-g-PEG and star polymers. Although natural polymers and hydrogels provide biodegradable substitutes, cytotoxicity and distribution efficiency still present difficulties.

Hybrid systems, which combine nanoparticles with natural materials or polymers, are a potential new field that will require significant study and development in the years to come. Resolving existing issues, such as improving intracellular trafficking and gene cargo stability, should be the top priority of future research. Potential safer and more effective therapeutic approaches for genetic abnormalities and illnesses might be realized through improvements in macromolecular architecture and careful functional group chemistry selection. The specific mechanism by which loaded genes are freed from vectors must be thoroughly studied since gene unpacking is crucial to the transfection process as a whole. Furthermore, creating intelligent vectors with the ability to discharge their gene contents in a regulated and timely way is essential to creating next-generation gene-delivery vectors.

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Chapter 9

Applications of Biopolymers in Next-Generation Drug Delivery and Implantable Devices

Phool Chandra , Prakhar Varshney , and Neetu Sachan 

Abstract Biopolymers are emerging as green and safer substitutes for man-made materials in drug delivery and implantable devices in medicine. Their inherent biocompatibility, biodegradability, and lower environmental impact make them particularly valuable for biomedical applications. Over the years, advancements in material science and biomedical engineering have played a major role in shaping drug delivery systems based on biopolymers for controlled and targeted therapy. Some of the most prominent examples are chitosan, alginate, hyaluronic acid, poly (lactic-co-glycolic acid) PLGA, and silk fibroin, which have shown immense promise in formulating novel drug carriers, nano-based delivery systems, and tissue engineering scaffolds. This chapter discusses the broad applications of biopolymers, especially in stimuli-responsive and customized drug delivery systems. Both biopolymers blended with nanotechnology and 3D printing methods are explored, with the benefits of more effective therapeutic effects by enhanced bioavailability of the drug, reduced side effects, and increased patient compliance. Regulatory implications, existing limitations, and future prospects for biopolymer-based systems are also discussed with emphasis on novel smart biomaterials and their relevance in the clinical context. With the rising need for patient-friendly and environmentally friendly medical solutions, biopolymers offer a promising route for the creation of next-generation therapeutic platforms. This chapter is intended to present an overview of their functional characteristics, modifiability, and expanding role in contemporary drug delivery and implantable technologies.

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1 Introduction

Biopolymers are naturally occurring polymers formed from microorganisms, plants, and animals, all of which are renewable resources from the environment. Biopolymers are the best choice for applications in medicine since they are both biocompatible and biodegradable [1]. Biopolymers, unlike synthetic polymers, provide structural and functional equivalents to natural tissue, lowering the potential of an adverse immune response. Biopolymers can be roughly classified into three basic types. They include the substances hyaluronic acid, alginate, and chitosan [2]. Collagen, gelatin, and silk fibroin are examples of proteins. Polyesters: Polycaprolactone (PCL) and polylactic acid (PLA). Biopolymers are made from renewable resources; they are environmentally friendly and sustainable [3]. For example, PLA is made from corn starch, whereas chitosan is made from the shells of crustaceans. They are environmentally favorable alternatives to conventional plastics because of their renewable nature, which reduces dependency on fossil fuels [4]. Synthetic polymers are stable and have tunable mechanical properties, but they are not biocompatible or biodegradable, which causes long-term environmental problems. Biopolymers, on the other hand, are safer for use in medicine since they naturally break down into non-toxic byproducts. The necessity for non-toxic, biocompatible materials that can improve biological functioning makes their use in biomedicine necessary [5]. They are perfect for use in tissue engineering, drug delivery, medical implants, and diagnostics because of their inherent ability to interact with the biological system without triggering immune response-based reactions. In the development of implantable devices and next-generation medication delivery, biopolymers are at the forefront [6]. Their biodegradability and capacity to form into multifunctional structures such as hydrogels, thin films, and nanoparticles allow for regulated and targeted drug release, increasing therapeutic activity while reducing adverse effects. Biopolymers reduce the risk of chronic inflammation and rejection by providing biocompatible and resorbable materials in implantable devices that are completely compatible with biological tissues [7]. Because of these qualities, they are ideal for developing advanced medical equipment and personalised treatment plans. Biopolymers are naturally occurring polymers produced from renewable feedstocks or by biological systems. Their biocompatibility, biodegradability, & functionalization capabilities have garnered significant interest in biomedical applications [6]. The need for non-toxic, biocompatible materials that can maintain biological functions has made the usage of biopolymers in biomedicine necessary. Their inherent ability to interact with biological systems without triggering undesirable immune responses makes them suitable for several uses, including medication delivery, tissue engineering, medical implants, and diagnostics [8].

Sustainable and biodegradable materials, including biopolymers, are becoming more and more necessary in biomedical applications due to growing environmental concerns and the growing demand for green products in the healthcare industry [9]. Traditional synthetic polymers are made from non-biodegradable, non-renewable petrochemical resources, which leads to significant environmental issues because of their non-biodegradability and the creation of hazardous byproducts [10]. On the other hand, biopolymers which are made by microorganisms or from renewable feedstock, offer a green substitute that adheres to the circular economy and green chemistry concepts. Because they reduce the carbon footprint of polymer manufacture and dependency on fossil fuels, biopolymers are environmentally beneficial [11].

Because they are biodegradable, they break down into innocuous byproducts, reducing pollution in the environment and making garbage disposal simpler. They are particularly crucial in medical applications where large quantities of disposable products, such as sutures, wound dressings, and drug delivery systems, are used [9]. Because biopolymers are inherently biocompatible, there is less chance of immunological reactions when they are used in implants and medical equipment. Patient safety is increased by the fact that their breakdown products are often non-toxic and easy to metabolize. This property is critical in systems for drug delivery and implant devices where long-term biocompatibility is required for therapeutic success [6]. Biopolymers exhibit great functional diversity due to their chemical heterogeneity and the ability to be tailored to specific biological uses. They can be engineered to have controlled mechanical properties, bioactivity, and degradation rates, allowing them to be used in a wide range of clinical applications such as medication delivery, tissue engineering, and regenerative medicine [2]. Chitosan and alginate are utilized in wound healing and drug delivery systems, whilst polylactic acid (PLA) and polycaprolactone (PCL) are employed in biodegradable sutures and orthopedic implants, respectively. The use of biopolymers facilitates the reuse and recycling of biomedical materials, promoting a circular economy [12]. Future developments in green synthesis and microbial fermentation technologies are increasing the production of biopolymers' scalability and affordability. Future research is expected to focus on developing next-generation biopolymers with enhanced functionality, such as self-healing, stimuli response, and personalized medicinal applications [13]. Biopolymers will be at the forefront of biomedical materials science in the future, spearheading the development of environmentally friendly healthcare solutions due to their sustainability, biocompatibility, and functional adaptability [6].

2 Types of Biopolymers Used in Biomedical Applications

Biopolymers are often classified into two categories: Natural biopolymers are polysaccharides, proteins, and nucleic acids originating from organisms like bacteria, plants, or animals [14]. Artificial biopolymers are produced through microbial fermentation or chemical synthesis, such as polylactic acid (PLA) and polyglycolic

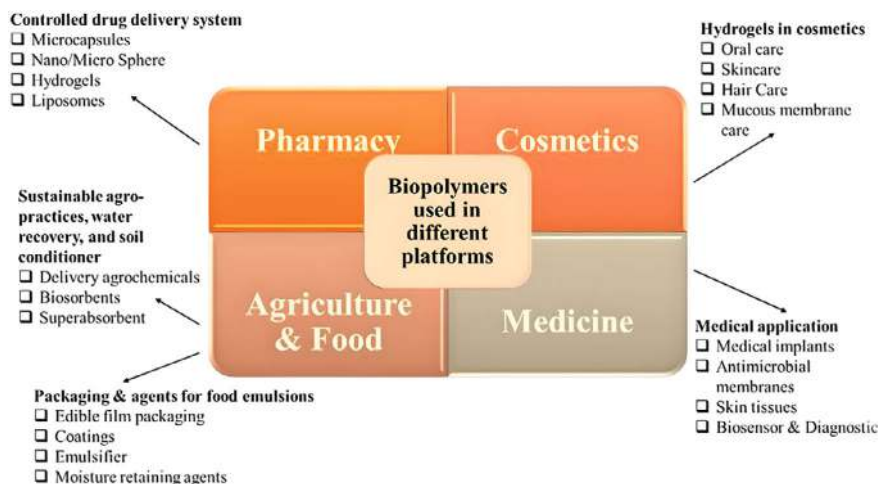


Fig. 1 Applications of biopolymers in different platforms

acid (PGA). Biopolymers have different applications in different platforms such as medicine, pharmacy, agriculture, food, and cosmetics (Fig. 1) [3].

2.1 Natural Biopolymer

As they come from living organisms, natural biopolymers are inherently biocompatible and biodegradable. Typically derived from plants, animals, or microorganisms, they are widely used because of their bioactivity and structural resemblance to the extracellular matrix [15]. Such as polysaccharides, their ability to crosslink and form hydrogels, as well as their biocompatibility and bioactivity, polysaccharides, including chitosan, alginate, and hyaluronic acid, are used extensively [16]. They have been used as scaffolds in tissue engineering, drug delivery formulations, and wound healing. Proteins with exceptional mechanical properties and biocompatibility for use in soft tissue engineering and wound dressing include collagen, gelatin, and silk fibroin [17]. The most abundant protein found in human tissues, collagen, is widely used in skin scaffolding and regeneration. Polyesters have mechanical properties and variable degradation rates; biodegradable polyesters such as PLA and PCL are employed in tissue engineering and medication delivery systems [18]. PLA is especially popular in 3D-printed bone regeneration scaffolds. New applications include nucleic acid-based biopolymers used in precision medicine and gene therapy. These biopolymers are vital for the production of mRNA vaccines, as well as enabling personalized medicine delivery [19].

2.2 *Synthetic Biopolymers*

Chemical synthesis and fermentation by bacteria are two approaches for producing synthetic biopolymers. To meet specific biological applications, they can provide adjustable mechanical properties, regulated degradation rates, and the insertion of functional groups [20]. Polylactic acid (PLA) is a polymer that breaks down made from renewable sources. PLA's ease of manufacture and biocompatibility make it ideal for orthopedic implants, drug delivery systems, as well as sutures. Polyglycolic acid (PGA) is widely employed in tissue engineering scaffolds and absorbable sutures due to its quick biodegradation and high tensile strength [3]. PCL (polycaprolactone) degrades more slowly than PLA and PGA, making it useful for medication delivery and long-term implants. Its biocompatibility and flexibility make it ideal for application in tissue engineering, particularly nervous tissue regeneration. Polyhydroxyalkanoates are microbial polyesters with varying biocompatibility and mechanical properties [6]. They are gaining recognition for their applications in medication delivery, tissue engineering, as well as biodegradable medical equipment. The synergy between synthetic and natural biopolymers enables the development of hybrid systems that can combine the mechanical strength and functionality of synthetic polymers with the bioactivity of natural chemicals. Biopolymers are important to the advancement of biomedical equipment because of their versatility [21].

2.3 *Hybrid and Composite Polymers*

By mixing two or more chemically distinct components at the molecular or nanoscale level, hybrid biopolymers go one step further. Strong contacts, occasionally even covalent connections, are used to blend the organic biopolymer with an inorganic phase (such as metal oxides or ceramics) or another polymer to create a new material with capabilities beyond basic additive effects [22]. New optical, electrical, or catalytic properties that are not present in the separate components can be produced by this tight molecule interaction. A biopolymer matrix (such as collagen, PLA, or chitosan) reinforced with fillers like natural fibers, nanoparticles, or other polymers is what composite biopolymers are often made [23]. To increase mechanical strength, thermal stability, or barrier qualities while maintaining biodegradability and biocompatibility, the reinforcing phase is physically distributed throughout the biopolymer matrix. Synergistic interactions in composites improve the performance of each component without necessarily forming new chemical bonds [24].

3 Patents on Biopolymers in Next-Generation Drug Delivery and Implantable Devices

Biopolymers have emerged as a promising class of materials for next-generation drug delivery and implantable medical devices due to their biocompatibility, biodegradability, and tunable physicochemical properties [25]. Developments in polymer engineering have allowed the creation of smart biopolymer-based systems that increase medication stability, release kinetics, and therapeutic results. Furthermore, biopolymer-based implanted devices integrate better with biological tissues, lowering immune reactions and increasing patient compliance [26]. Given the increased interest in this sector, numerous patents have been filed worldwide, indicating extensive research and invention. Table 1 provides a curated collection of patents involving biopolymers in drug delivery and implantable medical devices, emphasizing crucial details such as patent number, title, assignee, and proposed application areas [27].

4 Applications in Next-Generation Drug Delivery

By giving precise control over the timing, location, and mode of drug release in the body, next-generation drug delivery devices are revolutionizing therapeutic approaches. Stimulus-responsive drug carriers, controlled and sustained release systems, and customized/targeted drug delivery platforms are three significant advancements in this field [36].

4.1 Controlled and Sustained Release Systems

Systems for controlled and sustained release are made to keep a therapeutic substance at a constant level in the body for an extended period [36]. These systems can maintain plasma drug levels within the therapeutic window of a restricted range by formulating medications that are released at a predetermined, constant pace (ideally by zero-order kinetics), avoiding trough-induced sub-therapeutic dosing and peak-induced side effects [37]. Drugs are uniformly dispersed within a polymer matrix that either breaks down over time or creates room for drug diffusion, or they might be encapsulated inside hydrogels, nanogels, or microspheres. This approach reduces systemic toxicity, improves patient compliance, and lessens the need for repeated dosing. Long-acting implants can be utilized as drug reservoirs, constantly releasing the medicine locally. This is especially useful in post-operative or chronic disease scenarios [38].

Table 1 Patents related to biopolymers in implantable devices

Patent number	Title	Application area/key features	Publication year	References
US20240238600A1	Telemetry overuse reduction in an implantable device	The executable components include a communication component configured to set up a telemetry relationship with an external device and exchange data associated with sensed physiological data or therapy as well as an authorization component configured to determine whether the outside device is authorized to communicate with the IMD, whereby the communication part is further configured to disable the telemetry conjunction with the external device and prevent additional	2024-07-18 Pending	[28]
US12138463B2	Facilitating the trusted pairing of an implantable device and an external device	Systems, apparatus, techniques, and computer-readable storage media for enabling trustworthy pairing between an implanted medical device (IMD) and an external device are described. In one form, an IMD consists of a housing designed to be implanted into a patient, memory, and circuitry within the housing, and a processor that runs executable components stored in the memory	2024-11-12 Active	[29]
US7742816B2	Multichannel communication for implantable medical device applications	As detailed herein, an implantable medical device (“IMD”) is configured to facilitate concurrent multiple-channel data transmission with one or more additional devices in a patient-specific body area network. The IMD, and maybe other devices in the body’s local area network, can facilitate multiple channels communication with an unlimited number of other IMDs implanted within the same patient’s body. Furthermore, one or more of the active data communication streams may be full-duplex. Such embodiments can be flexibly designed to enable alternative data communication interfaces and/or modulation schemes if necessary to suit the specific application or operating environment	2010-06-22 Expired	[30]
US10653817B2	Method for producing an implantable ligament and tendon repair device	Biopolymer compositions and blends are described, as well as the use of benign solvent solutions to construct biocompatible scaffolds and surgically implantable devices for use in promoting and assisting soft tissue repair	2020-05-19 Active	[31]

(continued)

Table 1 (continued)

Patent number	Title	Application area/key features	Publication year	References
US10751185B2	Treatment of skeletal voids with an implantable substrate hydrated with bone marrow concentrate	The invention relates to a bone void filler with a scaffold or matrix. The scaffold or matrix could have a porous inorganic matrix component as well as a 3D-printed implanted device. The bone void filler may comprise a biological component including cells, some of which can produce extracellular matrix that resembles natural bone tissue. The bone void filler may contain an organic matrix, like an organic biopolymer, which promotes cell retention and makes the scaffold and matrix mouldable. The bone void filler may contain growth factors as well as cytokines. The bone void filler may contain a clotting agent	2020-08-25 Active	[32]
JP2025014001A	Implantable depot for controlled release of therapeutic agents	The current invention provides a depot for relieving post-operative pain by releasing a therapeutic drug in a regulated and continuous manner. In other cases, the depot may have a treatment area containing an analgesic compound and a control region containing a bioabsorbable biopolymer or a release agent mixed with the polymer. The releasing agent can be set to dissolve when the depot is placed in vivo, creating a diffusion opening in the control zone. The depot can be designed to be implanted In vivo at a treatment site & release the therapeutic agent while there for three days or more	2025-01-28 Pending	[33]
US20240261084A1	Scaffolds for bone-soft tissue interface and methods of fabricating the same	A device for regenerating musculoskeletal tissue that includes a scaffold made up of fibre layers that are designed to provide rigidity to the scaffold in the form of increased tensile as well as compressive resistance, as well as one or more other layers designed to provide mechanical integrity and a suitable biochemical environment	2024-08-08 Pending	[34, 35]

4.2 *Stimuli-Responsive Drug Carriers*

A complex class of devices known as “smart” or stimulus-responsive drug carriers delivers their payload in response to particular internal or external inputs. These carriers offer “on-demand” drug release that is precisely correlated with the target tissue’s local environment by including responsive material in their construction [39]. The majority of inflammatory tissue and tumors have modest acidity. Drugs are released precisely where they are needed thanks to pH-responsive polymer-carriers, such as those having Ionizable groups, which are stable at physiological pH (≈ 7.4) but swell or break down at acidity (pH 5–6.5) [40]. Glutathione and other reducing agents are frequently found at high concentrations in the intracellular compartment, particularly in cancer cells. It is possible to design drug carriers with disulfide bonds to break down in these circumstances and deliver their cargo intracellularly. To produce localized medication release, overexpressed enzymes (such as matrix metalloproteinases in cancer) may cleave specific bonds within a carrier [41]. These carriers’ temperature, light, and ultrasound are activated by stimuli that are applied externally. Ultrasound can cause drug release by mechanical or thermal effects, light-responsive systems use particular wavelengths to start structural changes, and thermoresponsive systems release medications when mild heat is applied (as in the treatment of hyperthermia) [42].

4.3 *Personalized and Targeted Drug Delivery*

To localize the therapeutic agent at the exact site of disease while avoiding normal tissues, targeted and personalized drug delivery aims to customize the treatment to each patient’s unique biological profile. This method makes use of the most recent advancements in digital fabrication, bioinformatics, and nanotechnology [43]. Folic acid, peptides, or antibodies can be used to ligand-surface-functionalize carriers, which then attach to receptors that are overexpressed in disease cells. To improve cellular uptake and reduce systemic adverse effects, folate-functionalized nanoparticles, for example, are used to target cancer cells with high levels of folate receptor expression. Drug delivery devices can now be tailored to the patient’s anatomy and disease profile thanks to developments in 3D printing and microfluidics [44]. The precise shape of a tumor location or tissue defect can be accommodated by these patient-specific implants or patches. To better treat diseases, personalized platforms can be designed to release many therapeutics simultaneously, such as immunotherapy or gene therapy, in addition to chemotherapy. Real-time tracking of medication release and therapeutic response is made possible by several next-generation carriers that combine therapeutic and diagnostic capabilities. Adaptive treatment plans can be adjusted based on the patient’s response, thanks to the combination feature [45].

5 Role of Biopolymers in Implantable Devices

Because of their biocompatibility, controllable degradation, and ability to interact with biological tissue, biopolymers are essential to the design and functionality of implantable devices. Three interrelated categories can be used to broadly classify their applications. Biopolymer composites in different biomedical fields (Fig. 2) [2].

5.1 Biodegradable Scaffolds for Tissue Engineering

Until the body can regenerate its tissue, biodegradable scaffolds made from biopolymers offer transient, three-dimensional frames that allow for cell adhesion, proliferation, and differentiation. These scaffolds decompose gradually, allowing host tissue to replace them without the need for a second procedure to remove the implant [46].

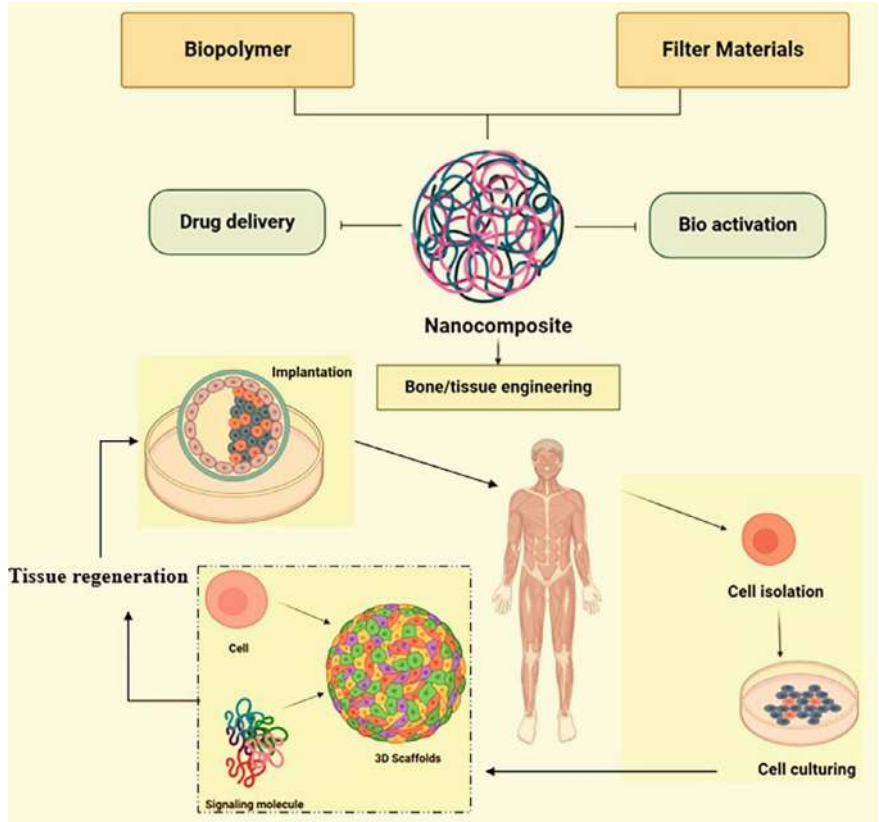


Fig. 2 Biopolymer composites in different biomedical fields

Collagen, gelatin, and chitosan are examples of biopolymers that closely mimic the natural extracellular matrix. Tissue regeneration is facilitated by their fibrous structure and metabolic signals. Scientists can alter the rate of scaffold disintegration to match the rates of tissue regeneration by adjusting the molecular weight, crosslinking density, and polymer composition [47]. Most frequently produced by techniques like electrospinning or freeze-drying, scaffold design offers interconnected porous networks that facilitate the movement of waste products and nutrients while providing transient mechanical strength for tissue support. Growth factors or medications can be injected into biodegradable scaffolds and released gradually to promote vascularization and healing [48]. For example, calcium phosphate can be added to a collagen-based scaffold for bone regeneration to improve osteoconductive; the scaffold will gradually break down as new bone tissue grows [49].

5.2 Smart Hydrogels and Injectable Matrices

Intelligent hydrogels are hydrophilic networks of crosslinked polymers that swell, contract, or degrade in response to specific stimuli (such as pH, temperature, or enzymes). They can be used as matrices that can conform to irregular tissue flaws because they are injectable & minimally invasive. In reaction to local environmental cues, the hydrogels can be engineered to release growth factors or encapsulated medications [50]. For instance, in the inflammatory, slightly acidic pH milieu of injured tissue, a hydrogel may transport its contents more quickly. Many innovative hydrogels are designed as injectable precursors that solidify at the implant site to form a gel that matches the shape of a tissue defect [51]. This feature reduces surgical trauma and recovery time for patients. Injectable matrices can be designed to offer localized and sustained release of medicines for infection prevention and tissue repair by controlling the crosslinking density or polymer chemistry. Dynamic bonds, reversible covalent or supramolecular interactions, are designed into some hydrogels so that the material can self-heal after minor injury while maintaining its structural integrity over time [52]. For example, a hydrogel based on chitosan that gels when it comes into contact with bodily fluids can be employed as a matrix for the administration of anti-inflammatory medications and stem cells for cartilage restoration [53].

5.3 3D-Printed and Nanostructured Implants

Implantable devices with highly customized geometries and micro-/nanoscale structures are now feasible thanks to advancements in 3D printing and nanotechnology [54]. These implants can be customized to better integrate with the surrounding tissues and fit the anatomy of the individual patient. Biopolymers such as hydrogels, poly (lactic acid) (PLA), and polycaprolactone (PCL) can be printed into

complex, patient-specific shapes using bioprinting techniques [55]. The fit and functionality of implants are improved by this precise customization. Cell adhesion and proliferation are enhanced by the inclusion of nanoscale features (such as surface nano-topographies, nanofibers, or nanoparticles). Additionally, nano-structuring can improve mechanical characteristics and speed up host tissue incorporation [56]. By combining different biopolymers and additives, 3D printing enables the creation of implant regions with varying mechanical characteristics, bioactivities, and rates of degradation. To promote tissue repair and prevent infections, implants can also be functionalized with bioactive molecules, such as growth factors or antibacterial chemicals. Additionally, drug release kinetics can be modulated by nanostructured surfaces to produce localized, long-lasting therapeutic effects [57].

For example, a 3D-printed PCL scaffold with hydroxyapatite nanoparticles integrated can be designed for bone tissue engineering, where the controlled deterioration allows for the gradual replacement of natural bone, and the nanostructured surface encourages osteointegration [57].

6 Advancements and Challenges

Although 3D printing and nanotechnology have accelerated the development of biopolymer-based implantable devices, there are still many obstacles to overcome. A thorough explanation of these developments and the issues that still need to be resolved is provided below. These developments and difficulties show how the field of implanted device research is constantly evolving [58]. 3D printing and nanotechnology together provide previously unheard-of possibilities for customization and functionality, yet maintaining biocompatibility and regulatory compliance remain formidable challenges. The secret to maximizing these next-generation therapeutic platforms will be to overcome present constraints through continuous innovation and interdisciplinary cooperation [59] (Table 2).

6.1 *Integration with Nanotechnology and 3D Printing*

Recent breakthroughs in nanotechnology have enabled the fabrication of implantable devices with nanoscale features that promote drug release, cell adhesion, or cellular interface behaviour similar to the extracellular matrix found in nature [60]. Nanofibrous scaffolds can be made utilizing techniques such as electrospinning and nanopatterning to increase their mechanical properties and bioactivity. Simultaneously, 3D printing technology, particularly bioprinting, has dramatically expanded the ability to make implants tailored to each patient [61]. This combination allows for the layer-by-layer construction of complex structures using biopolymers such as hydrogels, poly (lactic acid) (PLA), & polycaprolactone (PCL). These approaches enable exact regulation of mechanical properties, porosity, and degradation rates, allowing implants

Table 2 Advancements and challenges for applications of biopolymers in next-generation drug delivery and implantable devices

Application area	Advancements	Challenges	Examples	References
Nanostructured and 3D-Printed Implants	Advanced 3D bioprinting technology can provide patient-specific, customizable implants; nanostructured surfaces that encourage tissue integration and cell adhesion; and multi-material printing that enables gradients in mechanical characteristics and degradation profiles	Expensive, complex manufacturing, and difficulties scaling up Providing stability and long-term biocompatibility following implantation; Regulatory obstacles to clinical translation	Nanostructured biodegradable implants with regulated porosity; 3D-printed scaffolds made of polycaprolactone (PCL) with integrated hydroxyapatite nanoparticles for bone repair	[70, 71]
Injectable Matrices and Intelligent Hydrogels	Stimuli-responsive hydrogels that shrink, inflate, or disintegrate in response to environmental stimuli; minimally invasive, injectable systems that adjust to irregular tissue defects; and mechanical properties that can be adjusted and self-healing for prolonged release	Quick clearance or potential immunological reactions. Complexity of dual/multi-stimuli responsive system formulation. Stability and reproducibility in the complicated In vivo environment	Injectable chitosan-PEG hydrogels that are sensitive to pH and temperature, self-healing hydrogels that control medication delivery during wound healing	[72, 73]
Tissue Engineering Biodegradable Scaffolds (Implantable Devices)	The capacity to integrate growth factors or bioactive signals for improved healing; scaffolds that replicate the natural extracellular matrix (ECM) (collagen, gelatin, chitosan); and customizable breakdown rates to correspond with tissue regeneration	Maintaining consistent cell integration and vascularization, controlling immunological reactions to scaffold materials, and striking a balance between mechanical strength and regulated biodegradation	Growth factor-loaded porous gelatin matrices; electrospun collagen and chitosan scaffolds for cartilage and bone regeneration	[73, 74]
Customized and Focused Medication Administration	Surface functionalization for cell-specific uptake (e.g., using peptides, antibodies, or folate); Customizable platforms based on microfluidics and 3D printing. Theranostic systems that connect current imaging and treatment	Inter-patient heterogeneity in target receptor expression, high production costs, complex manufacturing processes, and regulatory concerns with personalized medicine	Dual-purpose theranostic carriers, patient-specific 3D-printed medication delivery implants, and folate-conjugated nanoparticles for cancer	[75, 76]

(continued)

Table 2 (continued)

Application area	Advancements	Challenges	Examples	References
Stimuli-Reactive Drug Transporters	“On-demand” release that is triggered by external (temperature, light, ultrasound) or internal (pH, redox, enzymes) stimuli. Systemic toxicity is decreased by localized medication release. Using nanotechnology in conjunction with focused control to improve targeting	High specificity and avoiding premature release, potential toxicity or complexity of intelligent materials, manufacturing scalability, and regulatory obstacles	Light-triggered carriers based on azobenzene moieties; disulfide-linked redox-responsive nanoparticles; and pH-sensitive micelles for tumor targeting	[39]
(Next-Gen Drug Delivery) Controlled and Sustained Drug Release	The creation of matrix systems with zero-order release kinetics, such as hydrogels, nanogels, and microspheres; longer therapeutic levels with fewer doses; improved patient compliance; and fewer adverse effects	Risk of dose dumping if release mechanisms malfunction; Variability in drug release due to patient differences as well as In Vitro/In Vivo variations; Optimization of drug stability in the matrix	Drug depots embedded in matrices, PLGA-based nanoparticles, and hydrogel-based devices that release medications gradually over several days	[77, 78]

to be created to fit the anatomical and functional needs of individual patients [3]. The combination of nanotechnology and 3D printing allows for zones on a single implant to deliver drugs, give structural support, or actively interact with host tissues. Despite these benefits, there are still challenges to overcome in scaling these technologies, making them reproducible, and achieving harmonic integration among many types of materials with varied chemical and physical properties [62].

6.2 Biocompatibility and Regulatory Considerations

Biocompatibility poses a significant challenge for implanted materials. Preferred biopolymers are biodegradable and have low toxicity; the addition of nanoparticles as well as innovative 3D-printed scaffolds, adds complexity [63]. In addition to promoting tissue integration and regeneration, these devices must avoid causing unwanted immunogenic reactions. Long-term interactions with tissues, degradation products, and possible cytotoxicity necessitate thorough in vitro and in vivo investigations [64]. Regulatory authorities that include the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) have strong rules in place to assure the security and efficacy of implanted devices. To ensure satisfactory results across production batches, the requirements require rigorous preliminary studies, quality control, and standardized testing methodologies [65]. The development of standardized methodologies has lagged behind rapid advances in nanotechnology and additive manufacturing, posing a significant barrier to clinical translation. As a result, current research strives to create strong regulatory structures that can accept these revolutionary technologies while also improving material performance [66].

6.3 Current Limitations and Future Perspectives

Despite significant developments, various challenges still hinder biopolymer-based devices for implants from being extensively used. The inability to predict and control long-term degradation rates & mechanical behavior in the complex In Vivo environment is a major drawback [67]. Variability in patient biology can lead to non-reproducible results, and it is currently difficult to combine various functionalities (e.g., medication administration with structural scaffolding) in an engineering setting. Furthermore, advanced manufacturing methods like high-resolution 3D printing and nanofabrication with nanoscale precision can be prohibitively expensive and difficult to scale [68]. Future directions include developing smart, sensor-embedded devices that provide real-time input on implant function, creating hybrid materials that combine the benefits of natural and synthetic polymers, and improving computer modelling to forecast implant behavior. The next generation of implanted devices will have improved safety profiles, more therapeutic efficacy, and more accuracy

thanks to continuous interdisciplinary research and changing regulatory norms. This will pave the way for genuinely personalized medicine [69].

7 Conclusion

Their incorporation into next-generation drug delivery systems and implantable devices has resulted in significant improvements in precision, safety, and treatment efficacy. Controlled and sustained release systems of biopolymers have been found to deliver stable therapeutic drug levels over long periods, minimizing dose frequency and adverse effects. Simultaneously, stimulus-responsive drug carriers that respond to certain internal (e.g., pH, redox, enzymatic) or exterior (e.g., temperature, light, ultrasonic) stimuli have enabled on-demand and localized drug release, increased targeting while minimizing systemic toxicity. Furthermore, personalized and targeted drug delivery strategies via surface functionalization and patient-specific fabrication employing 3D printing hold the potential of individualized therapy tailored to a patient's unique biology and illness condition. In the field of implantable medical devices, biopolymers are transforming tissue engineering and regenerative medicine. Biodegradable scaffolds mimic the extracellular matrix, providing temporary support for tissue regeneration while releasing bioactive chemicals. Smart hydrogels and injectable matrices build on this concept by offering minimally invasive solutions with stimuli-responsive properties that may be tailored for controlled, site-specific therapeutic release. In parallel, advances in nano-structuring and 3D printing have led to the creation of implants that are not only patient-specific but also have optimized bioactivity and mechanical qualities to better integrate with host tissues.

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Chapter 10

Cutting-Edge Drug Delivery Technology (3D and 4D) by Employing Biopolymers

Selcan Karakuş and Emine Elif Güzel Meydanlı

Abstract Modern drug delivery systems now require biopolymers due to their adjustable, biodegradable, and biocompatible characteristics. This chapter examines their function in different drug delivery strategies, with a focus on developments in three-dimensional (3D) and four-dimensional (4D) biopolymeric structures. In addition to a summary of the many drug kinetic models that control treatment efficacy, important facets of drug loading and release mechanisms are covered. Stimulus-responsive biopolymers that allow for targeted and regulated drug release are given particular consideration. The chapter also discusses the preclinical and clinical uses of formulas based on biopolymers, especially in gene delivery and cancer treatment. Additionally, the safety profiles of these nanoformulations are evaluated by looking at their cytotoxic, genotoxic, and apoptotic effects. The importance of biopolymer-based carriers in next-generation therapeutic approaches is emphasized by the discussion of their potential for accurate and effective drug targeting.

Keywords Biopolymers · Drug delivery · Drug kinetic model · Cytotoxic · Genotoxic · Apoptotic effects

Abbreviations

3D Three-dimensional

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4D	Four-dimensional
DDSs	Drug delivery systems
NPs	Nanoparticles
CNTs	Carbon nanotubes
PGS NPs	Polyglycerol sebacate nanoparticles
MEX	Material extrusion
FFF	Fused filament fabrication
FDM	Fused deposition modeling
FFE	Fused filament extrusion
AM	Additive manufacturing
RM	Rapid manufacturing
ABS	Acrylonitrile butadiene styrene
PA	Polyamide
SCPL	Solvent casting and particulate leaching
TIPS	Thermally-induced phase separation
TEOS	Tetraethyl orthosilicate
PLA	Poly(lactic acid)
PCL	Poly(caprolactone)
PHA	Polyhydroxyalkanoates
PEG	Polyethylene glycol
PVA	Poly(vinyl alcohol)
OH	Hydroxyl
NH ₂	Amino
PA6	Polyamide 6
CO ₂	Carbon dioxide
-NH ₂	Amines
EPR	Enhanced permeability and retention
ROS	Reactive oxygen species
AI	Artificial intelligence
ML	Machine learning

1 Introduction

Biomedical research has attracted a lot of interest due to the growing demand for bio-based components, especially in the areas of wound treatment, tissue design, and drug delivery systems (DDSs). By depolymerizing to the nanoscale, long-chain, plant-based biopolymers have the potential to be used to produce high-strength materials, drugs, and beauty products. Compared to their synthetic rivals, their natural origins offer obvious benefits. Green products are potential possibilities for a range of therapeutic uses due to their low toxicity, biocompatibility, biological degradation, and sustainable environmental impact.

The limited pharmacokinetic parameters features, decreased bioavailability at the point of behavior, decreased solubility in water, and adverse reactions of modern anti-cancer drugs all work together to reduce their overall performance, hinder the results of traditional treatment such as chemotherapy, and threaten patient safety. Nanostructures with sizes and shapes ranging from 1 to 1000 nm can be encapsulated by modifying them with different functional groups, thus increasing the efficiency and performance of drug loading and nanodrug-delivery systems [1]. The application of nanodrug-delivery systems for drugs with improved pharmacokinetic profiles may help to lessen the drawbacks of conventional combined therapies. Biopolymer-based DDSs employ appropriate carriers and control drug release systems, transport mechanisms, and interactions with the human body's local environment to improve the therapeutic effect and ensure the safety of the drug.

By improving colloidal stability, biocompatibility, biodegradability, drug efficacy, and bioavailability, as well as enabling targeted delivery, nanotechnology has made it possible to control shapes and structures at a small scale, thereby enhancing bio-based DDSs. For DDSs, a variety of nanostructures have been investigated, including nanoparticles (NPs) [2], nanoemulsions [3], metal/metal oxide nanocapsules [4], carbon nanotubes (CNTs) [5], lipids [6], hydrogels [7], polymer composite hydrogels [8], copolymer NPs [9], liposome NPs [10], and biological substances such vesicles that are extracellular. DDSs can carry weakly soluble chemotherapy drugs to targeted sites, including cancer cells, for on-demand release without damaging the normal tissue around them. Figure 1 presents a schematic representation of DDSs.

Biopolymer NPs, such as liposomes, polymers, dendrimers, and micelles; inorganic NPs, such as metallic NPs, carbon nanomaterials, and magnetic NPs; and hybrid nanoagents, which combine co-polymers with polymer-inorganic particles to produce synergistic effects against cancerous cells, are examples of standard agents [11]. Biopolymer-based nanocarriers can shield the active components and substances from the complicated environment *in vivo*, preserving their therapeutic effects. Pharmaceuticals can be effectively carried across cell walls *in vivo* by carefully modifying the surface characteristics of nanocarriers, greatly increasing their therapeutic effect and extending circulation duration. Hydrophobic interactions, hydrogen-bonding, covalent-bonding, and electrostatic attraction can all be used by nanomaterials to encapsulate or bind drugs, creating extremely efficient nanocarriers systems.

Nanostructures are produced using a combination of the polymer and the drug they contain to successfully load and transport drugs that are poorly soluble in water while preserving stability throughout a range of metabolic conditions. Furthermore, nanodrugs can prolong the retention duration of pharmaceuticals and shield them from enzymatic degradation in the gastrointestinal system by binding to saliva or cells of the epithelial layer. It greatly improves absorption and bioavailability while extending drug delivery. One example is the development of polyglycerol sebacate nanoparticles (PGS NPs) by Sivanesan et al. that encapsulated the initial phase chemotherapeutic drug 5-fluorouracil (5FU) [12]. Both MDA-MB-231 and A549 cells showed lower cell viability (~40%), extended 5FU release, and 90.39% 5FU encapsulation performance with these PGS NPs, with MDA-MB-231 cells showing

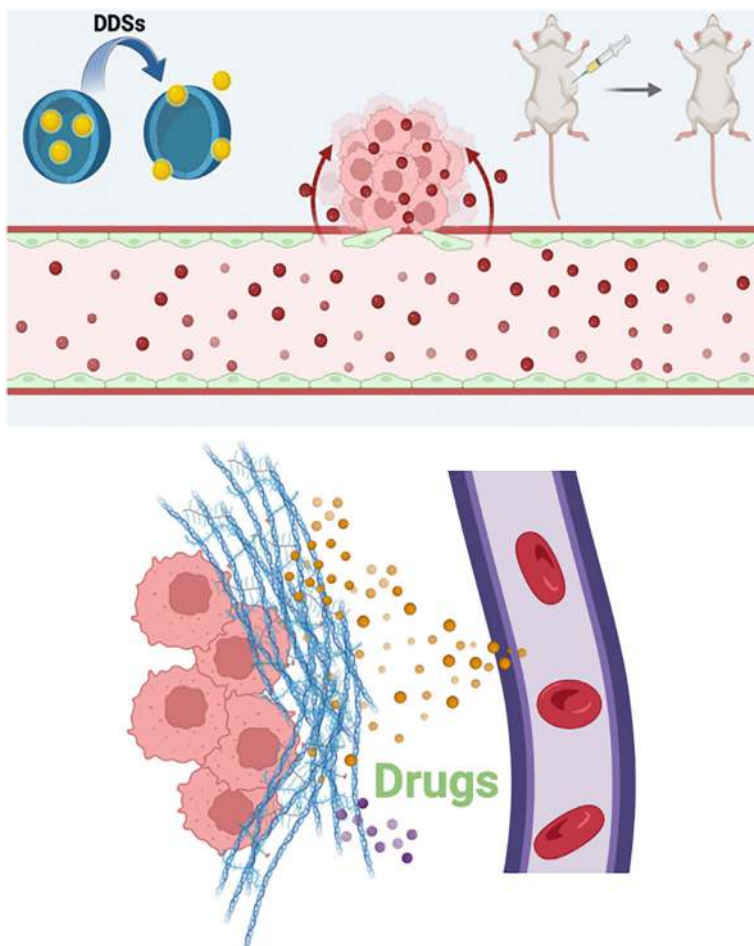


Fig. 1 Schematic diagram of drug delivery systems

higher sensitivity. Effective tumor-specificity was shown by enhanced caspase-3 activity, which was verified by apoptosis tests. Compared to free 5FU, 5FU-loaded PGS NPs have a higher *in vivo* bioavailability, which emphasizes the promise of nanocarriers in the treatment of cancer. An efficient method for resolving the challenges associated with drug administration is the application of bio-nanostructures in drug delivery systems. Plant-based biopolymeric materials such as cellulose and its related substances are the main source of organically produced biopolymers-based nanostructures. Strong hydrogen links between chains of cellulose and lignin's cross-linking function combine to produce an effective substance that may find use in therapeutic designs. Chemical and biological properties can be used to improve bioactivity and control drug delivery mechanisms. The incorporation of four-dimensional (4D) and three-dimensional (3D) structures of biopolymers-based nanostructures

into DDSs at the nanoscale allows for accurate and targeted drug delivery in addition to increasing therapeutic performance because of the greater surface areas. To overcome the drawbacks of traditional DDS manufacturing processes, like limited spatial control and low dimensional precision, new production techniques are crucial [9].

3D printing systems are generally more sustainable than conventional approaches because it produces a lesser amount of waste. These advantages have propelled major developments in 3D printing systems during the last 30 years, resulting in its extensive use in fields like as DDSs, orthopedics, dental care, and tissue engineering. Material extrusion (MEX) techniques, also known as fused filament fabrication (FFF), fused deposition modeling (FDM), or fused filament extrusion (FFE), are among the most widely utilized additive manufacturing (AM) techniques in medical applications [13].

- **Material extrusion (MEX) technique:** The MEX 3D printing approach deposits thin material beads by heating polymer filaments to a molten form inside a printer head (nozzle), which travels vertically across the build surface (X–Y axis). Beads harden and merge with the surrounding layers as they cool. The build platform moves in the Z-axis to make room for another layer to be deposited after a layer is finished. Until the item is completely produced, this process is continued. The final product's thermal, mechanical, and geometrical characteristics are greatly influenced by printing variables like as thickness of layers, nozzle temperature, and printing direction. When creating medical equipment that need exact matching and physical characteristics for effective functioning, these considerations are essential [13].
- **Fused deposition modeling (FDM) technique:** An additive manufacturing approach termed fused deposition modeling (FDM) is frequently utilized in bone tissue engineering because of its affordability, ease of usage, and capacity to produce personalized scaffolds. By using a heated nozzle to deposit thermoplastic polymers, layer by layer, this technique gives exact control over the mechanical characteristics, porosity, and shape. The solvent-free nature of FDM, in contrast to certain conventional manufacturing methods, lowers the possibility of toxicity and makes it safer for use in biomedical fields. It also makes it possible to regularly manufacture scaffolds that are biodegradable and biocompatible and specifically designed for the repair of bones. Because of its versatility in terms of substance choice and architecture, FDM is an important instrument for creating functional scaffolds that replicate bone's natural environment and promote better tissue integration, cellular adhesion, and proliferation [14].
- **Additive manufacturing (AM) technique:**

The method known as AM, or 3D printing, has become increasingly popular in a variety of scientific and industrial domains in recent years. At first, AM was mostly utilized for rapid prototyping, but as technology developed, it changed into an approach for creating the end product, also called rapid manufacturing (RM). A wide range of fields, including the development of products, wearable technology, technological products, and physically human–machine interface, are using AM today. AM, a group of processing techniques that produce items layer by layer, has emerged as an

essential innovation in biomedical field in recent years for the design and production of a variety of therapeutic products. Often termed 3D printing, these methods enable the direct production of personalized implants, prosthetics, and medical equipment from digital models. In the medical field, 3D printing offers two primary advantages:

- (i) It can produce patient-specific things without requiring for specific forms or instruments.
- (ii) It can produce intricate designs and forms that are challenging to accomplish using conventional techniques.
- (iii) Polymers based on thermoplastics are the main source of raw materials for these complex uses. Acrylonitrile butadiene styrene (ABS), polyamide (PA), thermoplastic elastomer, and PLA are some of the most widely used polymers for 3D printing. Each of these materials has unique mechanical and chemical properties that make it suitable for a range of uses.

Building on these developments, a number of biomedical manufacturing techniques, such as solvent casting and particulate leaching (SCPL), thermally induced phase separation (TIPS), gas-foaming, and freeze-drying, have been used to produce 3D polymeric scaffolds. These conventional methods, however, have a number of shortcomings that prevent them from being used therapeutically. Poor reproducibility, toxic solvents, low permeability, an inability to adjust the size of pores, and trouble producing complicated structural scaffolds are some of these drawbacks. To overcome these issues, 3D printing technology has become a feasible substitute in recent years. The process of additive manufacturing, also referred to as 3D printing, is able to quickly and precisely create complicated shapes from 3D model input. These methods for creating different platforms from hydrogels, biopolymers, nanocomposites, and nanofibres have drawn more and more attention from researchers. Nanofibers from different plant sources provide potential reinforcing capabilities in nanobiopolymer composites, with an emphasis on sustainable DDS solutions. Recently, nanocellulose has been used for developing DDS including hydrogels, aerogels, micro-polymers, nanobiopolymers, and sustained-release capsules. Cellulose, a common biopolymer, has shown performance in generating nanopolymers that improve the solubility of drugs and extend the duration of their bloodstream circulation. Additionally, because cellulose is hydrophilic, it inhibits opsonization, which promotes more effective accumulation of drugs in the specific areas. In 2022, Rimpý et al. focused on the production of 3D structures by modifying nanocelluloses obtained from rice and wheat straw with tetraethyl orthosilicate (TEOS) in order to develop new DDS [15]. In this study, the optimum scaffold structure contained nanosized cellulose, fluconazole, and solvent. Compared to unmodified scaffolds, nanocellulose-based scaffolds exhibited higher porosity, increased thermal stability, and mechanical strength (tensile strength). In ex-vivo vaginal permeation studies, these nanocellulose-based scaffolds provided better permeation of fluconazole and showed drug release up to 99%. They were also observed to be histologically safe and to have increased antifungal activity.

2 Role of Biopolymers in Drug Delivery Systems

To improve their efficacy and broaden their uses, researchers are designing innovative bio-based forms in 3D/4D printing methods. These complex structures form in reaction to external stimuli or environmental conditions, allowing for controlled release systems and preserving their structure for a predetermined amount of time. They reduce harm to nearby cells by precisely administering dosages to specific locations. It is possible to develop bio-based formulations that react to magnetic fields, ion concentration, pH, and temperature. chitosan, alginate, poly(lactic acid) (PLA), poly(ϵ -caprolactone) (PCL), polyhydroxyalkanoates (PHA), natural gums, polyethylene glycol (PEG), poly(vinyl alcohol) (PVA), gelatine, cellulose, and hyaluronic acid are common biopolymers used in their fabrication. Below, we provide examples of various biopolymers in DDSs.

Chitosan:

Since the 1990s, chitosan—a deacetylated derivative of chitin that Rouge initially investigated in 1859—has drawn interest from the biomedical studies. Chitosan is the second most commonly found biopolymer after cellulose. It is a linear biopolyaminosaccharide that is produced from chitin in an alkaline setting. It improves the functional features of bioproducts when mixed with polysaccharide and protein. Chitosan, which is abundant in hydroxyl (OH) and electron-dense amino (NH_2) groups, helps to stabilize and synthesize metallic nanostructures. It is perfect for altering surface properties and biodegradation profiles because of its mucoadhesion, solubility in water, and biodegradable properties which are made possible by the protonation of NH_2 groups in acidic conditions. It is formed up of N-acetyl-D-glucosamine and D-glucosamine units, and its characteristics change depending on molecular weight and degree of deacetylation. With it adheres to tissues, chitosan helps with wound healing, dental, and orthopedic DDSs. In addition to its cationic nature, it can bind to cell membranes, improving controlled release and drug absorption. Targeted treatments are further enhanced using chitosan nanoformulations. By encouraging the production of $\text{TNF-}\alpha$ by monocytes, chitosan also demonstrates its natural anti-cancer activities. It functions as an efficient anticancer agent due to its high bloodstream stability and low tissue accumulation. pH-responsive chitosan nanodrugs provide targeted DDSs in cancer environments, where anaerobic glucose metabolism reduces pH to ~ 5.5 , greatly increasing the efficiency of therapy [16]. The potential of chitosan, a naturally occurring biopolymer with antimicrobial, biocompatible, and biodegradable qualities, in tissue engineering was studied by Behrooznia et al. [17]. The work evaluated developments in 3D printing methods for developing chitosan-based scaffolds, including digital light processing, stereolithography, extrusion bioprinting, and inkjet bioprinting. These approaches rendered it feasible to regulate mechanical strength, porosity, and biological features, which made them compatible with a variety of cells, including cartilage, skin, heart, vasculature, and bone. This review emphasized the bright future of adaptable, flexible

chitosan scaffolds with enhanced biological activity as a result of advances in 3D printing technology and biological features.

Alginate:

Alginate, a polysaccharide that is both economical and biocompatible, is frequently utilized in wound dressings due to its low toxicological profile and mild crosslinking characteristics. Due to its reversible gel formation, it lessens discomfort during removal and encourages re-epithelialization. Alginate forms a hydrogel when exposed to calcium ions. β -D-mannuronic (M) and α -L-guluronic (G) acids are linked in a linear form to produce alginate. At pH 7.4, its G blocks have deprotonated, negatively charged carboxyl chains. With the help of multivalent cations like calcium (Ca^{2+}) ions, these groups allow crosslinking between neighboring polymer chains through ionic bonds. Ca^{2+} ions also improve alginate's hemostatic qualities in the healing process and are biocompatible at suitable doses. In 2025, the potential of the biopolymer alginate for 3D-printed wound dressings was the primary emphasis of Yalman et al. [18]. Alginate from *Cystoseira barbata* was extracted and purified for this study. Because of its anti-inflammatory qualities, humic acid was incorporated into a unique ink form to address a significant wound healing concern. Following the preparation of four biopolymeric ink solutions, the 3D-printed biomaterials were evaluated for their physicochemical characteristics, immunological response using inflammatory markers (IL-1 β , TNF α , and IL-10), and biocompatibility (MTT tests). The results showed that the recently developed HA-based alginate ink has a lot of potential for use in cutting-edge wound dressing applications.

Poly(Lactic Acid) (PLA):

In the biomedical sector, 3D printing has become a game-changing technology that provides creative answers for both patient-specific and commercial production. Because of MEX's adaptability, medical devices with exceptional strength and durability can be produced quickly, affordably, and with outstanding performance. MEX is very useful for applications like DDSs and prostheses. Both huge-scale manufacturing and specialized, patient-specific alternatives can benefit from MEX's ability to produce medical items with good strength and toughness at comparatively affordable prices and rapidly. PLA, PCL, and polyamide 6 (PA6) are thermoplastic polymer filaments commonly used in MEX 3D printing machines. Many of these biomaterials are biocompatible and appropriate for use in healthcare applications. The range of possible uses is expanded by the use of low-melting-point metallic substances in certain situations. This adaptability has sparked a great deal of study into MEX optimization for medical use, especially in the development of platforms for tissue engineering, DDSs, and customized prosthetics. According to this MEX 3D printing approach, biopolymers such as PLA and PCL have also been utilized in 3D-printed DDS. Using fused-deposition modeling, Korelidou et al. investigated implanted techniques for a biopolymer blend (PLA and PCL)-based DDS to develop reservoir-type systems for continuous drug release [19]. PLA and PCL membranes were produced by solvent casting, and cylindrical implants were 3D printed and loaded with tetracycline hydrochloride. The release of drugs was rendered feasible for a maximum

of twenty-five days by membranes with PLA/PCL solutions, whereas permeability was decreased by membranes with a lower PCL concentration. The size of the implant, drug content, and film thickness were important determinants of release. The implants demonstrated biocompatibility with endothelial cells and antibacterial efficacy against *S. aureus* and *E. coli* for a minimum of twenty-one days.

3 3D-4D Biopolymeric Drug Delivery Systems

To achieve accurate and controlled drug release, sophisticated, stimuli-responsive compounds are combined with sophisticated manufacturing methods for the development of 3D and 4D biopolymeric-based DDSs. Because of their biocompatibility, biodegradability, and adjustable chemical properties, a variety of biopolymers—such as natural gums, polyethylene glycol (PEG), poly(vinyl alcohol) (PVA), gelatin, cellulose, and hyaluronic acid—are frequently utilized in their design. Key instances of biopolymers used in these systems are listed below:

Natural Gums:

Emulsion gels have become interesting formulations for DDSs and 3D printing applications due to their improved stability, drug release abilities. They are appropriate for bio-ink solutions and prolonged release of drugs because they mix the benefits of gels and emulsions. But emulsion gels made entirely of peptides often exhibit low mechanical stability and low structural stability, which limits their wider use in therapeutic carriers and medical scaffolds. Natural gums and polysaccharides, like guar gum, taraya gum, chitosan, kappa carrageenan, Arabic gum, karaya gum, xanthan gum, and locust bean gum are frequently added to gels to improve their performance in order to overcome these difficulties. Gel stability, durability, and printing capability are enhanced by these biopolymers' strong intermolecular contacts, amphiphilicity, and self-associating qualities. A microbial polymer called xanthan gum is one of the best at forming polymer networks, enhancing viscosity, and maintaining colloid structures—all of which are critical for 3D-printable hydrogels and DDSs.

Emulsion gels have shown promise as bio-inks for 3D printing uses, according to Zheng et al. [20]. By crosslinking corn oligopeptide and natural gum (xanthan gum) to create corn oligopeptide-gum complexes, which functioned as Pickering stabilizers, they were able to successfully create edible emulsion gels for their study. The study investigated how the oil–water combination and xanthan gum amount affected the features of the emulsion gels that resulted from the interaction of maize oligopeptide and gum. The compact morphology of the corn oligopeptide-xanthan gum-stabilized emulsion gels allowed them to maintain a consistent, independent morphology for over sixty days, demonstrating exceptional stability. Deformation recovery, Shear-thinning behavior, and thermal stability all increased as one raised gum concentrations and oil–water proportions, according to rheological tests, which helped to increase printing quality and structure integrity. Consequently, emulsion gels with increased oil and natural gum contents showed better printing capability,

which made them ideal for 3D printing. These results enhance the use of peptide-polysaccharide combinations in emulsions for 3D printing by demonstrating the possibility of maize oligopeptide-xanthan gum-stabilized gels as functional bio-inks.

Polyethylene Glycol (PEG):

Polyethylene glycol (PEG) is a well-known plasticizer for biopolymers due to its high flexibility, hydrophilicity, dispersibility, low toxicity, and excellent biocompatibility. PEG improves the flow of material and integrity of structure while causing physico-chemical changes in the scaffolds that are generated, which in turn makes 3D printing easier. Furthermore, PEG makes biopolymers a viable addition for medical uses by increasing the biopolymer molecular chain's movement without sacrificing its ability to degrade or biocompatibility. The increasing popularity of AM for superior, cutting-edge applications was noted by Kumar et al. [21]. With an emphasis on surface properties, wettability, thermal behavior, and mechanical characteristics, they investigate the impact of PEG at concentrations ranging from 1 to 5 percent on 3D-printed PLA structures. PLA/PEG blends exhibited reduced crystallization temperatures and a lower glass transition than pure PLA. The addition of PEG considerably increased elongation at break and impact resistance while decreasing its tensile strength and Young's modulus. The contact angle decreased from 69° to 46° as wettability rose. PEG is a promising biopolymer for 3D-printed PLA since it provided the most favorable combination of form, mechanical efficiency, and processability among the studied compositions.

4 Drug Delivery Systems

4.1 Drug Loading

Drug encapsulation frequently uses agents, which provide important benefits for regulated and long-term drug delivery. Two main pathways exist for drug loading in nanoagents:

- (a) **Adsorption Mechanism:** A variety of drug-carrier interactions, including as covalent bonding, van der Waals forces, hydrogen bonds, or electrostatic interactions, can cause pharmaceuticals to be adsorbed onto the inner or outer surface of agents. Stability and effective drug encapsulation are made possible by these chemical interactions. Drug carry from bulk solution to active areas and subsequent penetration into the interior matrix comprise the adsorption mechanism in NPs. Drug loading efficiency is determined by the extent to which a drug interacts with the agent. Because of its ease of use, ability to preserve drug biological activity, and potential for stimulus-responsive carriers, the adsorption equilibrium approach is frequently employed for DDSs. To avoid surface deposition and leakage, it necessitates careful control of the concentration of drugs and frequently results in minimal drug loading. The choice of solvent affects loading

performance as well. Because solvent-drug relationships might interfere with adsorption, high solubility of drugs in a solution does not automatically improve loading.

- (b) Nano-scale effect: A nano-scale confinement effect occurs because nanoagents have smaller pores than significant crystalline nuclei. Because of this mechanism, drugs can be encapsulated in their amorphous state, which inhibits crystallization and speeds up the rate of breakdown after drug release.

The drug carrier's characteristics, including the amount of surface area, pore dimensions, functional groups, and volume of pore, mostly determine how much drug is loaded. Furthermore, the drug's physical and chemical features, including its pH level, solubility, and the binding capacity of the solvent, pharmaceuticals, and carrier. The loading capacity, distribution of drug within the vehicle, crystal structure, and the amount of drug released are all impacted by the loading technique chosen. The content and efficiency of drug loading are represented by the Eqs. (1–2):

$$\text{Content of drug loading \%} = \frac{\text{mass of drug in nanocarriers}}{\text{mass of nanocarriers}} \times 100 \quad (1)$$

$$\text{Loading efficiency \%} = \frac{\text{mass of drug in nanocarriers}}{\text{initial mass of drug}} \times 100 \quad (2)$$

Numerous approaches to drug loading into NPs have been investigated; each has unique benefits for stability and controlled drug release. These include one-pot drug loading and synthesis, adsorption equilibrium, incipient wetness impregnation, and solvent evaporation. Alternative methods include co-spray drying and fluidized bed dryers to improve drug encapsulation, as well as the use of liquid and supercritical carbon dioxide (CO₂), which provide mild loading conditions. While solid drug integration is possible with melt techniques and fluid bed hot-melt impregnation, more effective and quick drug incorporation is possible with microwave-assisted, milling-assisted, and ultrasonic-assisted loading [22]. These various methods offer designers flexibility in creating drug delivery systems that can be modified for stability, targeted drug release, and bioavailability.

4.2 Drug Release

DDSs are the delivery of active drugs to specific tissues or organs by a selected route of delivery. To ensure the highest performance with lowest toxicity, an efficient drug delivery system should keep the drug dosage within the therapeutic range. Key requirements for controlled release include site-specific targeting, accurate control of release, zero premature release, high drug loading ability, and excellent biocompatibility. Pharmaceuticals that are not well soluble in water frequently have problems with slower drug release rate, poor absorption, and safety. The utilization of high surface area inorganic NPs with multifunctional qualities, which provide improved

drug delivery efficiency and controlled release, is a viable strategy to solve these problems. The fundamental drug kinetic models and their mechanisms are presented in Table 1.

Drug release mechanisms can be divided into four groups based on how a drug gets out of a carrier:

- Ion exchange,
- Erosion,
- Dissolution, and
- Diffusion.

where t is the time, M_t is the drug's cumulative release over time t , and M_∞ is the drug's theoretical maximum release. n is the diffusion exponent, C represents the

Table 1 Different drug kinetic models and their mechanisms

Kinetic Model	Formula	Mechanism	Refs.
Higuchi	$\frac{M_t}{M_\infty} = K_H t^{0.5}$	Based on Fick's diffusion rules, the Higuchi model is frequently applied to drug release from insoluble material with pores	[23]
Hixson-Crowell	$\left(1 - \frac{M_t}{M_\infty}\right)^{\frac{1}{3}} = -K_{HC}t$	Formulations for erodible matrices	[23]
Baker-Lonsdale	$\frac{3}{2} \left[1 - \left(1 - \frac{M_t}{M_\infty}\right)^{\frac{2}{3}} \right] - \frac{M_t}{M_\infty} = K_{BL}t$	For spherical matrices such as microspheres and microcapsules	[24]
Ritger-Peppas	$\frac{M_t}{M_\infty} = K_0 t$	According to this model, the drug's diffusion mechanism from polymeric drug-loaded copolymers was evaluated	[25]
Korsmeyer-Peppas	$\frac{M_t}{M_\infty} = K_K t^n$	Drug release from polymer NP is described by this model	[26]
Zero-order	$Q_t = Q_o + K_o t$	Drug release is described by the zero-order model as concentration-independent, meaning that blood levels remain constant	[23]
First-order	$\log C = \log C_o - KT/2.303$	Drug release is concentration-dependent, according to the first-order model, which means that as the amount of drug drops over time, so does the release rate	[23]
Second-order	$1/C = 1/C_o + KT$	Drug release is described by the second-order model as being influenced by both the drug amount and an additional variable, like a metabolic enzyme or reacting agent, which results in an extra complicated, nonlinear release profile	[26]

drug's initial concentration at time t , the drug's released concentration at time t , K is the model release constant. f is the fraction of the drug released at time t .

4.3 Stimuli-Responsive Biopolymers

Stimuli-responsive biopolymers that are triggered by external stimuli such as magnetic fields, pH, and temperature. The pH value in various human tissues or bodily parts vary, which can start a particular DDS mechanism. The pH values of different tissues or organs, such as the stomach and liver, as well as conditions, such as inflammation, infection, and tumors, differ greatly. The two categories of stimuli-responsive DDSs are polyanions-polyacids and polycations-polybases. These systems can change their size in response to macro–micro level variations in pH. These changes include demicellization/micellization, swelling and collapsing, the process of dissolution and precipitation and changes in conformation. These systems are prepared in a variety of compositions. Organs, tissues, and cells can all experience variations in pH.

- Ionizable acid groups, such as carboxylic, phosphonic, or sulfonic acids, are found in the backbone of polyanions and polyacids. These groups get protonated at a low pH level, which unionizes the polymer chain. The polymer swells as a result of electrostatic repulsion when the pH rises because the acid groups release protons, which create negative charges.
- Basic groups including amines ($-\text{NH}_2$) are present in polybasic and polycationic DDS either as pendant groups or inside the polymer backbone. These systems absorb protons and acquire a positive charge in neutral or acidic conditions, which results in swelling because of electrostatic repulsion. These mechanisms are perfect for releasing drugs in conditions that are acidic, such as inside of cells or stomach.

The variations in pH that take place when NPs are absorbed by cells have drawn a lot of scientific attention in pH-responsive NPs. The blood's pH falls from about 7.4 to about 6.5 in the first endosomal region before falling even lower to less than pH 5 in the lysosomal region. The pH range of some extracellular areas, such as cancerous cells, is also rather acidic (6.4–6.8). Esters, amides, and imines, are examples of linkages that are stable in neutral solutions but dissolve at acidic pH level, releasing the imprisoned pharmaceutical by dissolving the NPs or their conjugated formulations through the breakdown of the polymer/matrix–drug bond. The assembly or disassembly of NPs and DDSs are driven by the pH-dependent interaction between ions and functional groups.

The ability to integrate pH-sensitive performs into different matrix structures makes nanomaterials with pH-responsive features particularly interesting since it makes it possible to create a variety of pH-responsive NPs. Controlling cellular uptake and cargo discharge is possible with these NPs because they may be engineered to alter in dimension, chemical composition, shape, disintegration, or carrier release

Table 2 Some examples of pH-responsive biopolymer-based nanoformulations used in DDSs

Nanoformulations	Results	Refs.
Carboxymethyl chitosan/sodium lignosulfonate microcapsules	At pH 9.0, cumulative release ranged from 80 to 61%. At pH 7.0, it slowed to 64%–50%, and at pH 5.0, it further slowed to 60%–42%	[28]
Mentha extract-Pectin/Alginate bio-nanocomposite	At pH 1.2, bio-nanocomposites show less weight loss while retaining their structural integrity. Phosphate interactions weaken cross-linking, as pH rises to 6.8 and 7.4	[29]
Imatinib loaded Fe ₃ O ₄ @SiO ₂ NPs	The NPs released 96% at pH 5.6 and 55% at pH 7.4, exhibiting pH-sensitive imatinib release behavior	[30]
Chitosan/carboxymethyl cellulose hydrogen Zinc oxide nanocomposite-graphene quantum dots	72% at pH 7.4	[31]
Doxorubicin (DOX)-loaded Starch/PVA/graphitic carbon nitride hydrogel	88% at pH 7.4	[32]
Escin metal nanocomposites-chitosan-graphene oxide and titanium dioxide	IC ₅₀ 22.68 µg/mL	[33]
Polycaprolactone-Polyamidoamine G4 NPs	12% and 9% of the drugs, respectively, were released at pH 5.0 and 6.0, but just 3% was released at pH 7.4	[34]

[27]. Therefore, as shown in Table 2, which offers examples of biopolymer-based nanoformulations utilized in DDSs, there is a great deal of promise for DDSs utilizing pH-responsive NPs.

5 Clinical and Preclinical Applications

• Biocompatibility and Biodegradability Advantages of Biopolymers

Biopolymers offer significant advantages over their synthetic counterparts due to their biocompatibility and biodegradability, making them ideal candidates for various biomedical applications. Biocompatibility facilitate perfect integration with surrounding tissues by minimizing inflammation and foreign body reactions, thus these polymers reestablish or maintain natural biological conditions, restoring function and providing structural support for the extracellular matrix. Acting as temporary scaffolds, biodegradable polymers support cell adhesion, proliferation, and differentiation. Since they are not toxic, biocompatible materials increase patient safety. On the other hand, controlled biodegradability aligns with tissue regeneration timelines, ensuring that the scaffold provides structural support only as long as necessary

before being resorbed by the body. In clinical manner, the use of biodegradable materials eliminates the need for second surgical intervention to remove implants, reducing patient risk and healthcare costs. Furthermore, biodegradability properties of biopolymers allow them to be tailored for DDS applications which enhances the efficacy of treatments and aligns with patient-specific needs. In addition to biodegradability, chemical structure and production technology of the biopolymer play a role for its use as a DDS. Among the natural polymers, chitosan is difficult to solubilize in body fluids; however, its mucoadhesive properties facilitate drug absorption across mucosal surfaces. Alginate, sourced from brown seaweed, forms hydrogels in the presence of divalent cations, enabling encapsulation and controlled release of therapeutic agents. Alginate microsphere scaffolds are used as DDS for rheumatoid arthritis. Sol-gel method technology is used for the controlled release of antibiotics, in this manner use of this technology made it possible to produce a topical delivery system that exhibits antimicrobial activity and prevents infection of hard-to-heal burn wounds [35, 36].

- **Personalized and Patient-Centered Drug Delivery Systems**

Personalized and patient-centered DDSs aim to tailor therapies to individual patient profiles. These approaches in DDS have several clinical benefits, such as providing optimal drug concentrations at target sites thereby improving treatment outcomes, reducing adverse effects by directing drugs specifically to diseased tissues and improving patient compliance by designing DDSs that align with patient preferences and lifestyles. Various delivery vehicles, such as polymeric micelles, liposomes, and nanoparticles, have been developed to achieve this precision. Nanotechnology has significantly contributed to the treatment of conditions such as cancer, genetic diseases, and chronic illnesses by cell-specific drug delivery. Moreover, advancements in personalized dosage forms and wearable medical devices allow treatments to be tailored to each patient's unique needs. The main potential of controlled drug delivery through nanomaterials is to increase efficacy by raising drug concentrations at the targeting site while simultaneously decreasing harmfulness by reducing target accumulation. When enhanced permeability and retention (EPR) effect is not suitable, nanomaterials are coated with a ligand as a targeting moiety which exhibits distinct targeting capabilities to direct selective binding of nanomaterials and reduce non-productive delivery.

Theranostics, a field combining therapy and diagnostics, exemplifies a significant advancement in personalized medicine, allowing for targeted cancer treatment based on real-time monitoring of the tumor environment. By incorporating diagnostic components, such as imaging agents or targeting ligands, into these delivery systems, clinicians can monitor drug distribution and accumulation and treatment response in real-time, enabling customized adjustments to the treatment plan [37–39].

- **Targeted Drug Delivery in Cancer Treatment**

Although traditional approaches such as surgery, chemotherapy, radiotherapy, thermal therapy, etc. have been developed and applied in cancer treatment, they have disadvantages and limitations. The use of nanobiopolymer-based DDSs is one

of the most prominent alternative approaches associated with effective cancer treatment. Nanobiopolymers offer numerous advantages in cancer drug delivery such as; (1) targeted delivery, (2) enhanced permeability and retention effect which is a characteristic feature of tumours where leaky blood vessels and impaired lymphatic drainage enable nanoparticles to accumulate and persist within the tumour tissue for an extended period, (3) controlled drug release, (4) encapsulation of diverse drugs which allows for combination therapy, where multiple drugs can be delivered simultaneously to achieve synergistic effects or overcome drug resistance, (5) reduced systemic toxicity, (6) overcoming drug resistance, (7) imaging and diagnostic applications and (8) personalized medicine. In fact, there are three types of targeting strategy of DDSs as passive targeting through EPR effect, active targeting using ligands and antibodies and stimuli-responsive drug delivery systems. Biopolymers in gene therapy and immunotherapy are being actively investigated. Exosome-based drug delivery systems are gaining attention as natural carriers due to their biocompatibility and ability to avoid immune responses. Innovations such as tumor-homing peptides, nanogels, and personalized cancer vaccines are providing hope for improved patient outcomes. Continued research and clinical validation are essential to fully harness the potential of these technologies in oncology [40, 41].

- Cytotoxic, Genotoxic, and Apoptotic Effects of Biopolymer-Based Nanoformulations

While biopolymers are generally considered safe, it is crucial to evaluate the cytotoxic, genotoxic, and apoptotic effects of their nanoformulations. The cytotoxicity is influenced by factors such as size, surface charge, and chemical composition. Smaller nanoparticles exhibit greater chemical reactivity, leading to increased production of reactive oxygen species (ROS), which can damage cellular components and reduce cell viability. For instance, certain metal-based nanoparticles have been shown to induce significant cytotoxicity by generating ROS, resulting in oxidative stress and inflammation. Nanomaterials can interact with genetic material, potentially causing DNA damage. Metal and metal oxide nanoparticles, such as silver, zinc, and copper oxide, have been found to induce DNA breakage and mutations. This genotoxicity may arise from oxidative stress mechanisms, where ROS interact with DNA molecules, leading to strand breaks and base modifications. Exposure to certain nanoparticles can trigger apoptosis which is often linked to mitochondrial damage and oxidative stress induced by nanoparticles [42].

- Role of Biopolymers in Gene Therapy

Gene therapy involves the introduction, alteration, or silencing of genes within a patient's cells to treat or prevent diseases. Biopolymers play a significant role in gene therapy due to their ability to deliver nucleic acids. The utilization of small RNA fragments, such as siRNA or miRNA, enables precise regulation of gene expression associated with pathologies. Antisense oligonucleotides (ASOs) are another application in which these short nucleotide sequences can effectively inhibit translational processes or initiate protein synthesis. Additionally, in mRNA technology, RNA acts as a carrier of genetic information, delivering instructions to cells regarding

producing specific proteins. This approach finds application in treating cancers and genetic diseases [43].

6 Challenges and Future Perspectives

In conclusion, despite advances in nanotechnological materials, the clinical applications of 3D and 4D biopolymer-based nanostructures in healthcare continue to face various challenges. One of the most significant limitations is large-scale nanomanufacturing, as the complexity of economically and efficiently producing materials developed at the laboratory scale on an industrial scale remains a major obstacle. Nanostructures with controlled drug release profiles require sustainable and environmentally friendly production techniques that must be optimized for personalized treatments. However, since newly developed nanomaterials still lack sufficient clinical data, they may not fully adapt to every patient profile and pose significant standardization limitations. Furthermore, the current state of nanotoxicological research has yet to reach the desired level, raising concerns about the long-term biosafety of biopolymer-based nanostructures. This situation contributes to potential biocompatibility-related risks, such as toxic effects and allergic reactions. When considering the performance of smart biopolymers that respond to physiological stimuli such as pH, temperature, and enzymatic activity, potential risks such as uncontrolled degradation, premature drug release, and the formation of degradation by-products—including their ability to cross the blood–brain barrier—must be carefully evaluated. In 4D systems, the maintenance of long-term mechanical stability is also a critical concern. Addressing these risks requires comprehensive preclinical and clinical validation processes.

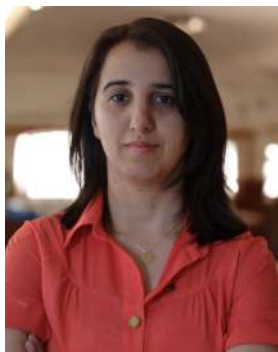
The integration of high-tech advancements, such as artificial intelligence (AI) and machine learning (ML), into biomaterial production and pharmaceutical research can help predict biopolymer behavior and optimize drug release kinetics, thereby minimizing the trial-and-error process. Green approaches in bio-nanofabrication, particularly advancements in 3D and 4D bioprinting techniques, will play a key role in improving reproducibility and efficiency. This could further enhance drug loading efficiency, targeted DDSs, and controlled drug release profiles. Additionally, biomaterials hold great potential in soft robotic systems due to their elastic and biocompatible nature. Bio-based robotic devices that respond to external stimuli and undergo shape transformations over time are being developed. These promising biomaterial-based approaches could be applied in dynamic prostheses designed for patients with muscle loss or in supportive implants for internal organs. Furthermore, the development of hybrid bio-nanomaterials is anticipated to enhance mechanical stability while maintaining biocompatibility. In the future, interdisciplinary research spanning chemistry, medicine, biomedical engineering, and mathematics will be instrumental in advancing next-generation DDSs-based platforms and significantly contributing to intelligent robotic systems.

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Chapter 11

Artificial Intelligence in the Development of Sustainable Biopolymers

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Melinda Arthur , and Stephanie Adomaa Aboagye 

Abstract Artificial intelligence (AI) is revolutionizing sustainable biopolymer development by expediting material discovery, optimizing production processes, and improving material performance. Through advanced machine learning (ML) techniques, researchers can analyze vast chemical datasets to design biodegradable polymers with tailored properties. AI-driven approaches have facilitated the identification of innovative materials, such as chitosan-based composites, with enhanced mechanical and antibacterial characteristics. Additionally, the use of AI facilitates the automation of biopolymer production processes, including the evaluation of mechanical properties and programmable material synthesis reducing reliance on petrochemical-based resources. These advancements not only contribute to scalable manufacturing but also to the development of eco-friendly alternatives to conventional plastics, offering improved functional performance. Moreover, the integration of AI in sustainability drives innovations in biochemical production, energy efficiency and environmental remediation. Despite challenges such as dataset standardization and model refinement, AI holds immense potential to accelerate the adoption of high-performance biodegradable polymers, addressing global environmental concerns and advancing materials science. This chapter provides a comprehensive review of the

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current advances in AI applications for sustainable biopolymer production, highlighting key achievements, challenges, and prospects. By addressing global environmental concerns and propelling the field of material science for several applications, AI holds promise as a powerful tool for the widespread adoption of high-performance biodegradable polymers.

Keywords Artificial Intelligence • Biopolymers • Sustainability • Plastics

Abbreviation

AI	Artificial Intelligence
ML	Machine Learning
DL	Deep Learning
CNN	Convolutional Neural Network
VAE	Variational Autoencoder
FTIR	Fourier Transform Infrared Spectroscopy
NMR	Nuclear Magnetic Resonance
ESN	Echo State Network
PHAs	Polyhydroxyalkanoates
PLA	Polylactic Acid
PHA	Polyhydroxyalkanoate
PHB	Polyhydroxybutyrate
PHVC	Poly(3-hydroxybutyrate-co-3-hydroxyvalerate)
CMDL	Chemical Markdown Language
T _g	Glass Transition Temperature
SVM	Support Vector Machine
PCA	Principal Component Analysis
R ²	Coefficient of Determination
RMSE	Root Mean Squared Error
COD	Chemical Oxygen Demand
NFC	Near Field Communication
IoT	Internet of Things
AFM	Atomic Force Microscopy

1 Introduction

Global plastic production reached 413.8 million metric tons in 2023, with an annual growth rate of 5.8 since 2009. China remains the world's leading producer of plastics [1]. Unfortunately, over 50% of this production consists of single-use plastics that end up as waste [2]. Karan et al. [3] assert that the total global plastic waste produced

could build 2,269 replicas of the Great pyramids of Giza, containing 240 exajoules of energy which is equivalent to the global annual energy demand.

These polymers derived from petrochemical products, require 1.6 billion liters of oil for 380 billion plastic bags [4]. However, only 21% of this waste is recycled or incinerated, leaving 79% in the landfills or the environment. On the other hand, incineration of these synthetic polymers poses serious environmental issues owing to toxic emissions such as furans, biphenyls and furans. This is causing massive accumulation of these waste materials in oceans [5]. These plastics degrade into a few millimeters (<5 mm) contributing to about 5.25 trillion plastic pieces in the global oceans. These microplastics which are gaining attention have been found to enter the food chain via fish, salt, bear and bottled water [3]. Moreover, these plastics are estimated to take longer than 100 years to fully degrade which highlights the need for sustainable alternatives.

China's 2017 announcement to stop accepting international plastic waste for recycling has exacerbated the plastic waste problem, necessitating sustainable biopolymer solutions by the year 2030 [6]. Biopolymer development has evolved through three generations/phases. The first phase focused on increasing sustainability in the industry by reducing the petrochemical feedstocks with natural monomers from plants and animals by using blends between petrochemical products and bioplastic sources. However, these blends did not fully degrade. The second and third phase demonstrated bio-based monomers with opportunities to expand, diversify, and scale up production of new bioplastics with similar superior physical properties to petrochemical-based plastics [3].

Biopolymers are gaining traction in research and governance, providing a feasible approach to sustainability. They help reduce municipal solid waste, carbon dioxide emissions, and reliance on petroleum-based resources. Biopolymers have potential to be incorporated in several industrial applications including packaging, agriculture, medicine (e.g. drug delivery), and textiles [7]. Despite these advancements, biopolymers face limitations such as poor processability, solubility in water or common organic solvents have been observed. Therefore, optimizing biopolymer processes by considering functional ingredients, processing and environmental factors is imperative to position biopolymers as sustainable alternatives to traditional plastics [8].

The growing need for biopolymers requires more efficient and scalable manufacturing processing. Given the plethora of factors and its implications on the functionality, toxicity, and sustainability of the biopolymers, it is important to build robust workflow and models to guide production of these polymers. Malashin et al. [9] assert that minor fluctuations in temperature, raw material quality, and process parameters can lead to increased waste and changes inconsistencies in the desired product specifications. Therefore, continuous monitoring, precise control systems, and innovations in workflow optimizations are necessary to ensure consistency in product quality.

Artificial intelligence (AI) offers a promising solution to these problems by facilitating optimizing production, predictive modelling, and real-time data processing. Although there have been several successes in the development of biopolymers globally, transition from concept to actual execution has taken decades. This delay is due to

the time-consuming trial and error nature of physical experiments, requiring several funds, specialized skills, and extended time [10]. AI holds the key to resolving this cascade of resource misuse. With set goal being a new material with success metrics including functionality and characteristics, safety and cost, AI has potential to make informed decisions, make rapid and reliable predictions and promise continuous improvements that could make the expertise accessible to anyone at any time. With several data on produced polymers, AI could be the final piece in the puzzle to put into robust model to achieve desired properties for the biopolymers. This chapter provides comprehensive review of the use of AI techniques in the development of sustainable biopolymers. It looks at the trend of research in the implementation of AI in biopolymer development and future outlooks.

2 Polymers: Evolution, Classification, and the Shift Towards Sustainability

Polymers are high molecular weight materials that consist of repeating structural components called monomers which are naturally occurring or synthetically produced [11]. Polymers include linear, branched chains, and crosslinks of these monomers including nucleic acid, amino acids, saccharides, and fossil fuel carbon-derived units which are the most utilized. They either consist of homopolymers or copolymers. They are essential in several industrial applications owing to their durability, versatility, cost effectiveness, and low density. Polymers have revolutionized many aspects of our daily life, replacing traditional materials such as metals and glass. This has been vital in the development of industries such as automotives, aerospace, electronics, healthcare, and construction which make use of polymers such as rubber, plastics, and textiles [12]. Polymers can be classified into several distinct types based on their composition, properties, and applications. Thermoplastic and thermosetting polymers are the two primary categories of polymers, each with distinct properties and applications. Thermoplastics are characterized by their ability to be melted and reshaped multiple times, making them highly versatile and recyclable. Some examples include polyethylene and polystyrene [13]. In contrast, thermosetting polymers undergo a chemical change when heated, resulting in a rigid structure that cannot be remolded. Examples include phenol resins [14] (Fig. 11.1).

Interestingly, polymers have evolved from natural sources as far back as 1811 where Henri Braconnot began his pioneering work with derivative cellulose compounds. However, polymers gained prominence after the work of Herman Staudinger in 1919. Staudinger was the first to propose that high molecular mass materials consist of long covalently bonded molecules [15]. This work earned him the Nobel Prize in Chemistry in 1953. However, after its discovery, petroleum-based polymers took the limelight because of their abundant raw materials and superior polymerization capabilities, which yield materials with exceptional functionality. It

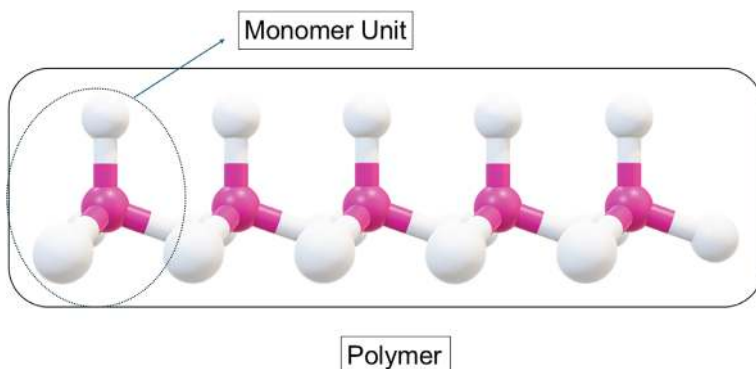


Fig. 11.1 General structure of polymers

served as a rich source of monomers like ethylene and styrene which are essential for synthetic polymer production. Due to the homogeneous structure, these monomers were easily polymerized into high molecular weight materials for varied applications. Over two million tons of synthetic polymers annually are predominantly derived from petroleum [16]. However, this trajectory has not been sustainable as polymers produced from these petrochemical sources such as polyethylene, polystyrene, and polypropylene are predominantly non-biodegradable posing significant environmental issues [17]. Current trends in the polymer industry reflect a significant shift towards sustainability, multifunctional, and advanced processing techniques shaping their future trajectory. There is rising demand for eco-friendly and sustainable biodegradable polymer materials to replace the toxic and unsustainable petroleum-based sources available [18].

3 Biopolymer: A Sustainable Alternative to Conventional Polymers

Biopolymers are polymers derived from natural renewable biomass resources such as plants, animals, and microorganisms. Therefore, they refer to materials whose monomers are sourced from living matter naturally or synthesized from these sources. Though there has been high interest and research in the area, there is constant confusion and debates on the use of the terms, biopolymers, biomaterials, bio-based polymers. Biopolymers are produced from renewable biological resources, including polysaccharides and proteins. They can be biodegradable or non-biodegradable [19]. Biomaterials also encompass materials intended for interaction with biological systems, which focus on medical applications [20]. Bio-based polymers are specifically derived from biomass, and these polymers are designed to replace petrochemical plastics and can be biodegradable, contributing to environmental sustainability.

3.1 Classification of Biopolymers

Biopolymers can be categorized based on their origin, structure and properties. They are broadly classified based on their production methods such as natural polymers (e.g.) Polysaccharides, proteins and synthetic biopolymers such as polylactic acid [21]. Based on the sources, biopolymers can be classified into plant-based sources, which include starch cellulose and proteins which are widely sourced from pulses, cereals, etc. Microbial sources which are derived from bacteria and fungi produced via fermentation processes such as polyhydroxyalkanoates (PHAs). Animal-based sources also include collagen and gelatin obtained from animals by-products. The use of renewable and waste biomass as feedstocks for biopolymer production is a key factor in reducing dependence on petroleum-based plastics.

3.2 Methods of Production

Biopolymers are produced via several methods including biological, chemical, and engineering approaches. Some of the recently used methods for producing biopolymers are as follows.

- (i) **Microbial Fermentation:** This involves the use of microorganisms such as bacteria and algae to synthesize biopolymers in a controlled environment. Some biopolymers produced via this method include polyhydroxyalkanoates and polylactic acid. A study by Gowda and Shivakumar [22] found that *Bacillus thuringiensis* was able to produce polyhydroxyalkanoates using agro-waste including rice husk, wheat bran, ragi husk, mango peels, and others. Mango peel yielded the highest polyhydroxyalkanoates—yield up to 51.3%. This was after 48 h at 37 °C. Polylactic acid was also produced from the fermentation of ricotta cheese whey and pear pomace using *Lactobacillus casei* and *Lactobacillus farciminis* [23]. Similarly, plastics can be engineered to produce bioplastics such as poly urethane and cellulose-based polymers [24]. Genetic engineering and metabolic engineering can be used to optimize microbial strains to produce biopolymers with desired properties. Some advantages of the process include high efficiency and ability to produce tailored biopolymers with specific properties, however the cost requirements can often be a barrier.
- (ii) **Extraction from Natural Sources:** Biopolymers can be obtained from natural resources including plants and animals. For example, cellulose, starch and proteins are commonly extracted from plants while chitin and chitosan are derived from crustaceans and insects [25]. This provides an abundant source for renewable resources; however, the quality of the biopolymers may differ depending on the source.
- (iii) **Chemical Synthesis:** This involves polymerization of biobased monomers to produce biopolymers. This method is used for producing polylactic acid derived from fermented biomass. It is produced via the ring opening polymerization

of lactide [26]. This method of production allows for precise control over the structure and properties of the biopolymers. However, reliance on fossil-based catalysts and high energy requirements presents drawbacks.

- (iv) **Advanced Manufacturing Techniques:** They include the use of 3D printing, electrospinning, and compression molding to produce biopolymers and process them into their final products. For instance, 3D printing has been used on biopolymers like PLA and PHA to produce biomedical devices and packaging materials [27]. Electrospinning also is used to produce nanofibers from biopolymers. These techniques provide flexible and precision over biopolymer-based products, however, the high cost and expertise required limits the use of these technologies.

3.3 Advantages and Challenges of Biopolymers

One of the significant advantages of biopolymers is their ability to degrade naturally in the environment, reducing plastic pollution. The biodegradation process involves microbial action, which breaks down the polymer into carbon dioxide, water, and biomass [28]. Many biopolymers such as PHAs and chitosan are also non-toxic and compatible with human tissues making them ideal for biomedical and food applications [29]. Biopolymers also exhibit a wide range of mechanical and thermal properties, depending on their structure and production methods. For example, PHAs can be tailored to have elastomeric or rigid properties [30]. Biopolymers like PLA and starch-based films have good barrier properties such as oxygen barrier properties though reinforcement is needed especially for starch-based films for moisture barrier properties. This makes them suitable for packaging applications [31].

Despite these advantages, biopolymers often face challenges related to scalability, cost and performance compared to conventional plastics [32]. Due to the lower investments in biopolymer industry compared to the petroleum-based packaging materials, the processing and end products of these biopolymers are more expensive than the petroleum counterparts. Another disadvantage also comes from their mechanical limitations, which involves the lack of durability and poor performance of some biopolymers such as starch polymers having poor moisture barrier properties. This makes their applications limited and requires several modifications in terms of modification techniques including cross-linking strategies to improve their functionality. This also has some implications for the processing and scalability of these processes.

3.4 Emerging Trends in Biopolymer Research and Applications

There have been recent advancements in polymer science which are addressing these challenges via several approaches.

- (i) Blending and composite formation—Combining biopolymers with nanomaterials or other biodegradable polymers to enhance their mechanical strength and functional properties [33]
- (ii) Enzyme engineering—Optimizing enzymatic processes to improve the yield and efficiency of biopolymer synthesis [34]
- (iii) 3D bioprinting and biomedical applications—The use of biopolymers in regenerative medicine, tissue scaffolding and bio-inks for 3D printing [35].

By varying the ratios and block types of the individual constituents as well as the processing techniques, the functional properties of the polymers are changed. Apart from them, other factors such as raw material properties, production costs, final design, and desired properties make for infinite possibilities to attain desired functionality for the biopolymers. This requires robust and innovative models that can help develop optimization and precision processes to produce desired biopolymers. This has been achieved by the incorporation of artificial intelligence into the biopolymer industry.

4 Overview of Artificial Intelligence

Artificial intelligence (AI) though popular currently is not a thing of today. As far back in 1956, the term artificial intelligence was proposed by John McCarthy at a conference at Dartmouth University [36]. That started a chain reaction into how machines could be developed and trained to simulate human cognitive abilities and even better. More attention was drawn to its potential after the world chess champion, Lee Sedol who was considered the greatest player of that decade, was defeated by Google's AlphaGo in March 2016 with a score of 4–1 in Seoul [37]. However, this wasn't the first time IBM's Deep Blue defeated Garry Kasparov, the reigning world champion in 1997 marking a significant feat in AI potential and subsequent development. Recently, AI has literally become a vital component in our everyday lives. It has in fact become a hot research area as every industry continues to assess its potential in several applications.

Artificial intelligence is a multidisciplinary technology that develops and trains machines to simulate human intelligence including critical thinking, decision making, and judgment. To accomplish this, it makes use of machine learning, emotional recognition, cognition as well as human and computer relations. It entails the compilation of knowledge and data varying from computer science, logic, STEM fields, and social sciences including psychology. This compilation and evaluation of knowledge has gained massive strides with the introduction of BP algorithm and the neural network. This was achieved in the 1980s where algorithm research based on artificial networks improved while computer hardware functions also developed. More applications came into the limelight with the introduction of mobile Internet [38]. All the same, deep learning introduced in 2012 also boosted artificial intelligence development. The major requirement for the development of AI that is relevant

and accurate has always been the need for a big data reservoir. Therefore, whatever study that has ever been done in the past years was not a waste of time at all, but essential for building robust and efficient systems for tomorrow. Then again with the introduction of Internet of Things, more data have accumulated in exponential amounts to fast track the development of AI data banks. Through the concept of the Internet of Things, the Internet has been expanded to physical items such as sensors and imaging systems that are connected to the Internet, which can also be used via smartphones and other intelligent devices to communicate via NFC, Bluetooth, and Wi-Fi.

Following the generation of big data for the AI database, the laws and methods to recognize or analyze the data set to make meaning of them were also needed. Therefore, researchers also developed AI algorithms which include sets of instructions that teach computers to learn and tasks that would typically require human intelligence. To make use of this algorithm, machine learning was developed to enable the computers to learn and analyze the big data before making decisions and even predictions. This has been applied in several fields including recommendation systems, speech and image recognition [39]. Image processing methods like computer vision were developed which uses algorithms to identify and analyze images. To make meaning and predictions out of the large data sets, machine learning performs clustering, dimensionality reduction, classification, and then prediction. The ways in which these processes are done categorize machine learning into four types that include reinforcement learning, unsupervised learning, semi-supervised learning, and supervised learning [36].

Reinforcement learning employs a reward-based approach where quality of actions is judged based on reward levels. This approach was derived from behavioral psychology. The concept of positive reinforcement originated by B.F. Skinner in his operant conditioning theory in 1930. He discussed that increasing the likelihood of behavior can be achieved by a rewarding stimulus and the opposite for punishment stimulus. This method of learning involves a trial-and-error approach to finding the best operation and behavior to gain the greatest return.

Unsupervised learning also makes use of data mining which involves extracting knowledge from a large data set by problem identification, data preparation, model building, evaluation model, and result evaluation. Some data mining technologies include classification, regression, clustering, correlation analysis, cause and effect test, association models, and prediction analysis [40]. It involves classifying data according to different properties without the use of data labels. Some methods of unsupervised learning include principal component analysis as well as k-clustering which makes use of orthogonal transformation and principal component analysis (PCA), respectively.

Supervised learning involves the use of data tags to train the model for it to make more accurate predictions. It makes use of classification and regression. Methods used in supervised learning include support vector machine and linear discrimination analysis [41]. Therefore, based on the trend and relationship between the database, it can make predictions on the continuous values. Therefore, the more data input, the more robust and accurate the prediction made.

Semi-supervised as the name indicates stands in between supervised and unsupervised learning. Therefore, it has data tags and data without tags. Some researchers have found that unlabeled data when used with a small amount of labeled data can improve learning accuracy. However, its application is limited due to the requirement of high expertise and cost of the labeling process.

With all these machine learning methods, computing power is the most important factor to ensure accurate and efficient use of artificial intelligence. This is because it requires deep learning algorithms such as restricted Boltzmann machine, convolutional neural network, and deep belief network to solve complex problems [42]. Current parallel computing processors developed by NVIDIA have revolutionized the AI industry as originally processed data which took months can be processed in a day.

4.1 Application of Artificial Intelligence

Upon the development and promise shown by artificial intelligence, it has been used in several industries to solve problems whiles creating economic benefits. AI has been applied to the automotive industry, health industry, media industry, finance industry, and recently in the material industry. Some applications include the introduction of self-driving or autonomous driving in the automobile industry, better market forecasting systems, and unmanned retail platforms such as Amazon Go which improve efficiency while reducing costs.

Among the industries actively incorporating AI into their processes, the biopolymer industry which forms a section of the larger material industry is actively incorporating artificial intelligence techniques in the development of sustainable biopolymer materials.

4.2 Artificial Intelligence in Biopolymer Development

The development of sustainable biopolymers is a critical step towards reducing the environmental impact of traditional plastics. However, the discovery and synthesis of these materials face challenges due to their chemical complexity, diverse feedstocks, and the need for precise characteristic tuning. The introduction of artificial intelligence (AI) has revolutionized the biopolymer industry by offering unprecedented avenues for material discovery, design, and optimization. AI has created a platform in which material intuition, experience, and the vast repository of data and knowledge have been encoded and embedded. These hold promise for continuous improvement making expertise readily accessible to anyone. This technology has been used in the prediction of optimal fermentation technologies, real-time monitoring of process parameters, and ultimately improved the efficiency of biopolymer production [24]. The incorporation of AI in biopolymer synthesis provides precise

control over the various processes and factors involved in the production to ensure consistent and high-quality biopolymer materials which can help reduce waste, optimize energy usage, and streamline logistics [9]. Machine learning algorithms, such as random forests and gaussian process regression, have been employed to model complex relationships between polymer compositions and their mechanical, thermal, and degradation properties.

Thanks to much research conducted on polymers throughout the years, large data sets which are reliable and cover several material properties exist to help AI techniques develop accurate models. Then again, the use of fingerprinting techniques presents thousands of descriptors from atomic to chain levels. All these data points are now generalizable and interpretable thanks to machine learning algorithms which can be used to map polymer fingerprints forming a strong basis for developing predictive models. Candidate materials for polymers have been proposed using inverse methods such as Bayesian optimization, evolutionary algorithms, and Monte Carlo schemes. To overcome the hurdles in realistic synthesis of these proposed polymers, virtual forward synthesis has been used as an emerging approach which has been used to digitally generate several possibilities of synthetically accessible polymers using easy to synthesize monomers inserting them into polymerization reaction templates. This approach involves several steps including screening the criteria based on the desired characteristics of the biopolymer. Based on these criteria, it launches an expansive search into large library of polymers produced through the method, using the large computed and diverse datasets to make predictions for polymers that qualify based on the desired outcome. These systems are required to be tested via physical experiments as benchmarks to verify the predicted characteristics which are described as a success if it meets it or is repeated if not. Therefore, AI presents a reliable pathway for successful transitioning from laboratory-scale to commercial scale synthesis.

5 AI-Driven Approaches in Sustainable Biopolymer Development

5.1 *AI in Discovery and Synthesis*

- **Predictive Modelling**

One of the most significant contributions of AI in biopolymer development is its ability to predict the characteristics of materials including their mechanical and barrier properties. These predictions enable researchers to identify promising candidates for producing sustainable and highly functional biopolymers with less time consuming and resource intensive experimental trials.

Graph neural networks have been successfully applied to predict properties of bioderived polymers. For instance, PolyAGM which is a machine learning algorithm used graph kernel methods to predict the thermal and mechanical properties

of bioderived ABA-block polymer thermoplastic elastomers [43]. Again, combining high throughput molecular dynamics simulations with machine learning models has been shown to efficiently predict glass transition temperature of biopolymers; for example, a dataset of 546 polymers, including 58 homopolymers and 488 copolymers, was generated using molecular dynamics simulations. These data were used to train a machine learning model that predicted the glass transition temperature with a mean absolute error of 19.34 K and an R2 score of 0.83. This approach significantly accelerates the discovery process, as thousands of polymers can be evaluated in seconds, whereas traditional simulations would take several years [44]. In other studies, multitask deep neural networks have been employed to predict the properties of polyhydroxyalkanoates (PHAs). Using experimental data for nearly 23,000 homo- and copolymer chemistries, these networks identify promising bioplastics that can replace petroleum-based plastics. For example, 14 PHA-based bioplastics were identified as potential replacements for seven commodity plastics, accounting for 75% of global plastic production. These models were made available through the polymer genome project, enabling widespread use of the biopolymer design [45].

The synthesis of biopolymers involves optimizing complex processes, such as monomer selection, reaction conditions, and polymer architecture. AI has emerged as a valuable tool for guiding these processes, enabling the design of materials with desired properties. In a recent study by Basdogan et al. [46], machine learning driven genetic algorithms were constructed to design polymer membranes for carbon dioxide separation from Nitrogen and Oxygen which could act as an efficient carbon capture and separation technology. The algorithm used literature data on gas permeability to train the models which were able to predict the performance of new polymers. This approach identified 20 new polymers out of 16,000 polymers derived using crossover and mutation functions for 100 generations, which were above both CO₂/N₂ and CO₂/O₂ upper bounds. It also found membrane materials with high transition temperature and specific functional groups such as pyridine to be promising. Furthermore, Bayesian optimization has also been applied to the design of sustainable epoxy resins. LASSO regression, which is a machine learning model was used to predict the properties and interpret relationships among the formulation components and target properties including the mixture of bio-based and petroleum components to derive desired mechanical and physicochemical properties [47]. Lastly, active learning methods have also been employed to guide the discovery of acrylate photopolymer compositions for additive manufacturing. Jain et al. [48] showed how the algorithm dynamically selects monomer ratios to build robust machine learning models that predict polymer properties such as Young's modulus and Shore A harness.

• Process Optimization

Machine learning has emerged as a powerful technology for optimizing biopolymer production processes. Rather than relying on trial-and-error approach used in traditional methods, Machine learning techniques including supervised, unsupervised, and deep learning algorithms have been successfully applied to analyze complex data generated during biopolymer production, identifying patterns and insights that are not easily observable through conventional methods [9]. In a recent study by Diment

et al. [49], Bayesian optimization was employed to fine-tune Aqua Solv Omni biorefinery to produce lignin–carbohydrate complexes which achieved high yields up to 15 wt.% with tailored biopolymer characteristics. Again, machine learning algorithms have been used to predict the mechanical properties of biopolymer composites, such as elastic modulus and critical fiber strength enabling the design of resistant materials [9]. This also extends to the optimization of process parameters and conditions such as the temperature, process severity and liquid to solid ratios to maximize yields and product quality [49]. Furthermore, AI has been used to engineer recombinant systems and optimize media conditions that achieved a sixfold increase in polyhydroxyalkanoates from *Bacillus cereus* 6E/2 [50]. Similarly, a graph variational autoencoder model was employed for the inverse design of vitrimeric polymers which are a new class of sustainable polymers with dynamic covalent networks [50]. This led to the development of polymers with desired glass transition temperatures and good functional properties. The use of AI in polymer design has also been extended to the development of biobased polymeric blends, which offer improved sustainability and reduced carbon footprint [51]. Lastly, a chemical markdown language (CMDL) was developed to enable the flexible representation of polymer structures and experimental data facilitating the integration of historical data into AI models. This approach has been successfully used for the design of novel ring-opening polymerization catalysts and co-polymer structures [52]. Therefore, by predicting the composition and mechanical properties of biopolymer blends, AI has enabled the creation of new materials with enhanced performance and sustainability.

5.2 *AI in Characterization and Quality Control*

• **Data-Driven Analysis Techniques**

Spectroscopy is a cornerstone of polymer characterization, providing critical insights into molecular structures and properties. However, the interpretation and analysis of spectroscopic data can be complex and time consuming. AI has emerged as a powerful tool to enhance the analysis of spectroscopy data enabling faster, more accurate and robust interpretations. Raman spectroscopy is widely used to identify types of polymers and analyze their structural characteristics. However, the analysis of this spectra can be challenges due to the overlapping peaks and environmental interference. Machine learning has been applied to improve the accuracy and efficiency of Raman spectroscopy-based polymer identification. Some studies found that machine learning algorithms such as Random Forest was able to classify polymer types based on Raman spectral data with a classification accuracy of 93.81% when tested on environmentally aged microplastics [53]. Other machine learning techniques including principal component analysis, K-nearest neighbors, and support vector machine for Raman spectroscopy also showed promise in improving resolution and speed of microplastic analysis [54]. Lei et al. [55] also introduced a

customizable machine learning approach for Raman spectroscopy achieving classification accuracies exceeding 95% even when spectroscopic data is downgraded to lower resolutions.

While Raman spectroscopy has been a focus of machine learning applications, other spectroscopy techniques like Fourier Transform Infrared Spectroscopy (FTIR) and nuclear magnetic resonance can also benefit from AI-driven analysis. Machine learning algorithms can be trained to extract features from FTIR and NMR spectra to predict polymer properties such as crystallinity, molecular weight, and degradation levels. These predictions can accelerate material development and quality control processes. Again, image analysis techniques such as scanning electron microscopy and atomic force microscopy provide high resolution structural information about biopolymers that can be significantly enhanced via AI by automating image processing, feature extraction and defect detection. De Oliveira et al. [56] showed that the use of computer vision techniques such as Mask RCNN and U-Net, to analyze the microstructure of biopolymer composites and was able to estimate mechanical properties like elastic modulus and critical length, providing valuable insights for material design.

Deep learning algorithms like convolutional neural networks have revolutionized image analysis by enabling automated segmentation and feature extraction. These techniques are particularly useful for analyzing complex polymer structures and identifying defects. Multiscale modelling approaches combine molecular-level simulations with image analysis to provide a comprehensive understanding of polymer structures. Zheng et al. (2024) used an innovative approach coupling molecular dynamics and simulations with graph variational autoencoder model (VAE) to design vitrimer chemistries with desired structural properties. Using dual graph encoders and latent dimension overlapping scheme, VAE had high accuracy and efficiency in discovering the novel vitrimers which was experimentally validated showcasing the framework as an exciting tool to synthesize sustainable and functional biopolymers.

• Real-Time Monitoring and Feedback Control

The application of AI for real-time monitoring and feedback control has evolved into a transformative approach, enhancing process efficiency, product quality and sustainability. Traditional methods often struggle with the complexity and non-linearity of biopolymer processing; however Artificial Intelligence offers advanced tools and computing advantages to handle these challenges. Koprinkova-Hristova and Palm [57] in his research on the complex and nonlinear bioprocess optimization to produce polyhydroxybutyrate (PHB) using echo state network (ESN) as a critic network within the frame of adaptive critic design for adaptive control. This approach increased the yield up to 14.28% from the initial outcome, while ensuring proper training of the critic network, even in the presence of noise. Alcantara et al. [58] also used a soft sensor based on Raman spectroscopy to the in-line monitoring of polyhydroxyalkanoates. This approach led to real-time collection of quantitative data on culture, nitrogen and carbon concentrations and cell dry weight without need for sampling with root mean squared errors from 0.03 to 7 g/L. It demonstrated the in-line

monitoring potential of Raman spectroscopy coupled with machine learning techniques. Other studies have shown the potential of combining deep neural networks with hybrid neural network workflows for process analysis, process monitoring and model predictive control [59].

5.3 *AI for Functional Enhancement and Tailoring*

- **Material Design and Customization**

Artificial intelligence is increasingly being applied in the design of sustainable biopolymers with targeted functionality. These models leverage vast datasets and advanced algorithms to predict material properties and optimize their design. In a recent study by Chen et al. [60], an all-natural plastic was developed using a support vector machine. The classifier was trained using 286 nanocomposites with varying cellulose nanofibers, montmorillonite nanosheets, glycerol, and gelatin prepared by a pipetting robot. The model selected a specific ratio for the different ingredients that had an A-grade nanocomposite film at a high success rate of more than 94%. The model was able to predict the resulting polymers in terms of their optical, thermal, and mechanical properties. Generative AI techniques such as generative adversarial networks are being explored for several biopolymer designs. These models can translate biological design principles into engineering solutions, enabling the creation of multifunctional and biodegradable polymers [61].

- **Performance Prediction**

Simulation models play a pivotal role in analyzing the feasibility and efficiency of biopolymer production processes. These models enable researchers to predict how biopolymers will perform under varied processing and environmental conditions which can guide optimization and scale up processes. Pozo-Morales et al. [62], assessed the production of polyhydroxyalkanoates integrated with wastewater treatment plants using a novel simulation tool. The model developed identified aerobic dynamic feeding process strategy, which is the internal growth limitation as the most favorable achieving a production rate of $0.226 \text{ kg of COD}_{\text{PHA}} \cdot \text{kg}^{-1}$ and reducing sludge production by 6%. Other simulations have been able to simulate the production of some biodegradable polymers such as PHBV, poly (3-hydroxybutyrate-co-3-hydroxyvalerate) while analyzing the nitrogen sources, oxygen partial pressure and substrate concentrations on microbial growth and poly accumulation. The role of valeric acid in improving the 3-hydroxyvalerate content of PHBV in enhancing biodegradability was highlighted [63]. Duvigneau et al. [64] also demonstrated the use of machine learning to predict PHBV composition and yield in real time, leveraging carbon dioxide measurements in exhaust gas to refine process conditions.

5.4 *Artificial Intelligence in Sustainability and Lifecycle Analysis*

• Environmental Impact Assessment

Artificial intelligence has been integrated into life-cycle assessment and has totally revolutionized the way environmental impacts are evaluated, offering precise predictions and optimizing sustainable practices. Machine learning models have been developed to predict the biodegradation of polymers in aquatic environments. For instance, a study used Morgan fingerprints and thermal decomposition temperature as input descriptors to achieve an R_{test}^2 of 0.66. The model identified structural features such as the substructure R-O-R in polyethers and polysaccharides positively influenced biodegradation, while molecular weight and aromatic rings negatively impacted it [65]. This approach helps in designing environmentally friendly polymers while providing insights into their environmental fate. Another study used Bayesian optimization to predict the decomposition degree of compost-degradable polymers. The model considered factors such as moisture content, degradation period and crystallinity, achieving high accuracy. This predictive tool is essential for optimizing material design and experimental conditions which ensures that biodegradable polymers meet environmental standards [66]. 3D molecular descriptors have also been shown to enhance prediction of chemical biodegradability. A study tested support vector machines (SVMs) and ensemble learning algorithms, to achieve an accuracy of 0.88 using 3D autocorrelation descriptors. These models are imperative to contribute to green chemistry and achieving sustainable development goals [67]. Convolutional neural networks and long short-term memory networks have been applied to predict biodegradability where it achieved an accuracy of 87.2% [68].

• Circular Economy Integration

The integration of circular economy principles with artificial intelligence techniques provides a transformative potential for upcycling, waste valorization, and design of end-of-life scenarios for biopolymers. Upcycling and waste valorization focuses on converting waste materials to high value products while minimizing environmental impact. Though complex, these processes can be enhanced using artificial intelligence analytics to provide predictive modeling, process optimization, and material design. Galluccio [69] introduces informational upcycling which makes use of computational methods and AI to address the complexity of reclaimed materials. For instance, the FoRWARD project demonstrates how the informational upcycling can be applied to wood waste in the Italian furniture industry. Again, Ayub and Ren [70] demonstrated the use of AI and response optimizer surrogate models to predict and optimize co-pyrolysis process. By evaluating models such as CatBoost Regressor and extreme gradient boosting, the optimal conditions for maximizing yield were identified showcasing the role of these techniques in valorizing mixed waste streams. Furthermore, Parveen et al. [71] asserts that the integration of AI-powered sorting technologies such as machine learning-based systems can improve the efficiency

of bioplastic recycling to ensure materials are correctly routed to their appropriate pathways.

6 Case Studies and Industry Applications of AI in Biopolymer Synthesis

Artificial intelligence has been applied in biopolymer synthesis, offering sustainable solutions to both laboratory projects to real-world industrial implementation. A summary of several studies of the applications of AI in biopolymers can be found in Table 11.1.

7 Challenges and Limitations in AI-Driven Sustainable Biopolymer Development

Though the inclusion of artificial intelligence has seen great successes, there are still several challenges that need to be addressed.

High-quality, labeled datasets are scarce in polymer science. Hindering the training of robust AI models. For instance, the development of biodegradable polymers like polyhydroxyalkanoates require extensive experimental data, which is often difficult to obtain due to cost and complexity of experiments [76]. Polymers exhibit diverse chemical structures and properties, making it challenging to create comprehensive datasets, which are often lacking. Therefore, to address this data scarcity, synthetic data generated from digital twins of production lines have been proposed. This approach can provide high-quality training data, especially in dynamic production environment where real data becomes obsolete quickly [77]. Other limitations include AI model struggle with the complexity of polymer behavior, especially in predicting long-term degradation and mechanical properties. Wilson et al. [72] found that while machine learning could predict the glass transition temperature of the biobased polymers, the accuracy is still limited with mean absolute errors ranging from 19.8 to 26 0.4 °C. Lastly while AI can optimize the production of bioplastics like PHAs in small-scale experiments, scaling up to industrial levels requires addressing issues like cost-effectiveness and process consistency [76].

8 Future Direction and Emerging Trends

One key area of interest in AI incorporation in biopolymer synthesis lies in synergies with other technologies to improve its impact. For instance, the integration of IoT with AI is being explored as it would allow for real-time monitoring of production

Table 11.1 Real-world applications of AI-driven biopolymer development

AI technique	Application in biopolymer synthesis	Findings	References
PolyID	Development of polyethylene terephthalate (PET) analogue	Model reduced the design space of renewable feedstocks enabling efficient discovery of performance biobased polymers. Also identified five PET analogues with predicted enhancements in thermal and transport performance from a pool of 1.4×10^6	[72]
Molecular dynamics and novel graph variational encoder model	Design of vitrimer chemistries with targeted glass transition temperatures	This led to the curation of a diverse dataset of one million chemistries, with Tg calculated for 8,424 of them through high throughput simulations. The framework also discovered novel vitrimers with desirable Tg values (323 K) beyond the training regime and was experimentally validated	[50]
Support-vector machine classifier and artificial neural network	Discovery of all natural plastic substitutes focusing on biodegradable alternatives	Developed a prediction model, to enable the prediction of the physicochemical properties of all-natural nanocomposites based on their composition and automates the design of biodegradable plastic substitutes	[60]
Multitask deep neural networks	Predict properties of bioplastics and identify PHA based replacements for petroleum-based plastics	The study developed multitask deep neural network characteristic predictors that utilized a data set of nearly 23,000 homo and copolymer chemistries to identify 14 PHA-based bio plastics as potential replacements for seven petroleum-based commodity plastics, which account for 75% of the world's yearly plastic production. This approach allows for efficient exploration of a candidate space of approximately 1.4 million bioplastics	[45]
Transformer models	Predicting thermal stability of collagen triple helices	The model used amino acid sequences with experimentally determined thermal stability to achieve accuracy similar to ProtBERT while having fewer parameters	[73]

(continued)

Table 11.1 (continued)

AI technique	Application in biopolymer synthesis	Findings	References
Machine learning – Deep neural network	Decomposition analysis of biodegradable PD/HDPE composites using machine learning techniques	The study found that the thermal decomposition of PD/HDPE composite material showed a significant dependence on the degradation temperature, with thermogravimetric analysis revealing that the actual percentage weight loss shifted to higher temperature maxima as the heating rates increased. Using a machine learning deep neural network approach, the research developed improved learning algorithms that achieved a near zero residual error (0.025) after over million iterations. Thus, the algorithms successfully predicted the thermal behavior of PD materials at higher degradation temperatures (600 to 1000 °C) with predictions closing aligning with experimental results	[74]
Deep neural network, gene expression programming, and optimizable gaussian process regressor	Evaluation of hemp bio-composite properties using machine learning methods	The study developed model for the compressive strength and conductivity of hemp bio-composite using three machine learning methods. The models demonstrated high prediction capabilities with deep neural network model showing the best performance for the compressive strength ($R = 0.9997$) and thermal conductivity ($R = 0.999$). It also used the Shapley Additive explanations to interpret models, revealing that the trends of input variables influencing the properties of hemp bio-composite were consistent with experimental studies	[75]
Machine learning and high-throughput molecular simulations	To predict the glass transition temperature of biopolymers	Combining machine learning with high throughput molecular dynamics simulations allowed for efficient sampling and characterization of the chemical design space for biopolymers. Again, it predicted the glass transition temperature of 546 polymers, including 58 homopolymers and 488 copolymers. The models achieved a mean absolute error of 19.34 K and R^2 of score of 0.83 in predicting the glass transition temperature using a machine learning model trained on the simulation data, indicating a strong correlation with experimental results	[44]

processes, data collection and process control. Again, collaboration with robotics and automation is a promising area for AI in biopolymer synthesis. Improved 3D printing processes can lead to enhanced mechanical properties of the biopolymers while having reduced material waste.

While AI offers significant benefits for sustainability its energy consumption during model development and deployment raises concerns. Policymakers are urged to promote energy-efficient AI models and invest in renewable energy infrastructure to mitigate these challenges. There is a need for further research on the practical implantation of AI-driven circular economy process.

9 Conclusion

The integration of artificial intelligence in sustainable biopolymer production has made significant strides in improving efficiency and functionality of these materials positioning them as viable alternatives to the petrochemical-based polymers. However, the full realization of their potential will depend on interdisciplinary collaboration, supportive policies and balanced regulatory frameworks. As these technologies continue to evolve, they will play a critical role in achieving sustainability goals and promoting a greener, more efficient manufacturing industry.

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Chapter 12

Recent Applications and Future Prospects of Biopolymer-Based Composites in the Food Industry

Heba G. R. Younis, Fatma Abdelrahman, and Hassan R. S. Abdellatif

Abstract Biopolymer-based composites signify a swiftly advancing domain in food science, providing sustainable answers to significant difficulties confronting the food sector. This chapter comprehensively reviews recent advances in biopolymer-based products and their uses in food processing. We investigate food-grade biopolymers' essential features, processing processes, and characterization methods, focusing specifically on protein-based composites, polysaccharide-based systems, and hybrid materials that include innovative reinforcing components. Using these materials in active and intelligent packaging systems has shown considerable enhancements in barrier characteristics, antibacterial efficacy, and shelf-life prolongation for diverse food products. Nanotechnology has significantly broadened the capabilities of biopolymer composites, allowing advanced delivery methods such as protein–polysaccharide complex nanoparticles and lipid–biopolymer hybrid structures that improve stability, bioavailability, and targeted release of bioactive compounds. The amalgamation of intelligent technologies with biopolymer composites has created stimuli-responsive packaging, enhanced sensing functionalities, and quality monitoring systems. Essential factors concerning safety evaluations, regulatory adherence, and environmental sustainability are examined, encompassing migration studies, toxicological assessments, and life cycle analyses that illustrate the diminished ecological impact of these materials relative to traditional alternatives. Our study indicates that biopolymer-based composites will persist in revolutionizing food packaging, preservation, and delivery systems, simultaneously addressing urgent environmental issues through biodegradable alternatives and sustainable processing methods. Future research should concentrate on expanding manufacturing techniques, improving material performance, tackling regulatory obstacles, and further incorporating smart technologies to fully exploit the promise of these promising materials in commercial culinary applications.

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Abbreviations

AgNP	Silver nanoparticles
AM	Acrylamide
CC	Calcium carbonate
CD/MOF	Carbon quantum dots-loaded metal–organic frameworks
CDs	Carbon quantum dots
CEO	Clove bud essential oil
CH	Chitosan
CHA	Catalyzed hairpin assembly
CNC	Cellulose Nanocrystals
CNC- CA	Citric acid-modified Cellulose Nanocrystals
CNCs	Cellulose nanocrystals
CO ₂	Carbon dioxide
CP	Chitosan/polyvinyl alcohol
CQDs	Carbon quantum dots
CSFETs	Chemical-sensitive field-effect transistors
CUR	Curcumin
3D	Three-dimensional
DART	Direct Analysis in Real Time
DO	Dissolved oxygen
ED	Esterification degree
FDA	Food and Drug Administration
GC-MS	Gas chromatography-mass spectrometry
GEL	Gelatin
Gly	Glycerol
GRAS	Generally Recognized as Safe
H ₂ S	Hydrogen sulfide
HPS	Hyperbranched polysiloxanes
HRM	Humidity-responsive materials
IP	Isoelectric point
LCA	Life cycle assessment
LCST	Lower critical solution temperature
LMP	Ligninmicroparticles
MB	Methylene blue
MLA	Pullulan with 10%
MOFs	Metal-organic frameworks
N ₂	Nitrogen
NA	Natamycin

NE	Nanoemulsion
NH ₃	Ammonia
NPG	Ethylene–vinyl acetate–glycidyl methacrylate
O ₂	Oxygen
OM	Overall migration
PANI	Polymers including polyaniline
PBAT	Polybutyleneadipate terephthalate
PBS	Poly butylene succinate
PBSA	Poly(butylene succinate-co-butylene adipate)
PE	Pectin
Pe	Pickering emulsion
PHAs	Polyhydroxyalkanoates
PHB	Polyhydroxybutyrate
PLA	Poly lactic acid
PPy	Polypyrrole
PSP	Purple sweet potato
PTh	Polythiophene
PTW	Photochromic transparent wood
PVA	Polyvinyl alcohol
PVA	Poly(vinyl alcohol)
RH	Relative humidity
SA	Sodium alginate
SP	Soy protein
ssDNA	Single-stranded DNA
TA	Tannin acid
UCST	Upper critical solution temperature
UPLC-Q/ToF	Ultra-performance liquid chromatography in conjunction with time-of-flight mass spectrometry.
WP	Whey protein
WPI	Whey protein isolate
WVP	Water vapor permeability
XG	Xanthan gum

1 Introduction

Meeting people's demands for food items that are safer, more sustainable, and last longer while addressing environmental issues is becoming more and more difficult for the food sector [1]. The global food industry, particularly in developing countries, is now unsustainable since the world population is anticipated to rise from 7 to 10 billion by 2050, with an annual increase of 70 million people, escalating the demand for food production by 70% [2]. Traditional food packaging methods, preservation, and delivery systems are being revolutionized by biopolymer-based nanotechnology.

The latest uses of biopolymer-based composites in the food industry are examined in this chapter, with special attention paid to developments that have greatly improved food safety, quality, and sustainability between 2020 and 2024 [3].

This chapter comprehensively explores recent advancements toward the applicability of biopolymer-based composites in the food industry. The scope covers several fields, including sensor technologies, encapsulation systems, active and intelligent packaging, and practical applications of foundational research. The main goals are to: (1) Analyze the structural features and functional attributes of different biopolymer composites that are pertinent to food applications, (2) Assess new developments in nanoscale delivery systems for bioactive compounds; (3) Evaluate how well biopolymer-based packaging materials perform in terms of prolonging shelf life and food quality monitoring; and (4) Talk about safety considerations and regulatory viewpoints for commercial implementation.

This chapter also aims to highlight future research topics for increasing possible uses and overcoming existing restrictions. Emerging developments focus on artificial intelligence integration in composite design, sustainable processing methods, and creating edible delivery vehicles with improved functionality. Significant focus is directed toward innovations, including incorporating artificial intelligence in composite design, sustainable processing methodologies, and creating effective food delivery systems.

2 Types of Biopolymers

Many biodegradable polymers are available in different areas and have various physical behaviors, attractive wettability and sorption properties, dissolving easily in different organic solvents and water. The wide applicability and the safety of biopolymers like chitosan, alginate, or pectin are confirmed by their acceptance in the pharmaceutical or food sectors and various biomedical applications. The safety of these biocompatible biopolymers originates from the fact they are *in vivo* degradation products of living plants or animals. On the other hand, the biodegradability of these biopolymers is also confirmed by *in vivo* studies, which showed that after their use as a medicine or food, they are completely metabolized by living tissue [4]. In the last few years, biopolymers have gained increased importance as biodegradable and bioacceptable biodevices for various medical applications. Many researchers deal with investigations into biopolymers as new classes of biocompatible materials from renewable sources, suitable for medical, pharmaceutical, and biotechnology applications. At the same time, recent studies are focused on the processing and modification of the structure of biodegradable biopolymers and their composites by biotechnological methods to increase biocompatibility and biodegradability. This research activates the advancement of novel technologies for obtaining biopolymers from renewable sources by biotechnologies. Biopolymers are derived from renewable resources, and they are biodegradable and biocompatible. They have the capacity

to supplant the synthetic polymers that are currently in use and are accumulate in the environment due to their significant resilience to deterioration [5].

Biopolymers are classified into two categories: polymers that occur naturally and synthesized polymers. Biopolymers that exist naturally are synthesized by organisms, such as polysaccharides, proteins, and polyhydroxyalkanoates, whereas synthetic biopolymers are artificially produced polyesters, polyamides, polyurethanes, polyethers, and polyesters. Natural and manufactured biopolymers, together with their advantages, drawbacks, and future prospects, have been enhanced based on physicochemical characteristics, biodegradation, biocompatibility, and environmental and economic issues. Biomedical and environmental applications of natural and synthetic biopolymers are described as well. Biodegradable polymers are important for the prevention of environmental pollution. The rapid growth of plastic waste and the increasing scarcity of landfill space have led to a growing demand for biodegradable materials. Biodegradable plastics, which polymerize by chemical or microbial methods, and biodegradable polymeric materials of renewable resources, naturally occurring biopolymers, interest researchers from different fields. Biopolymers are essential components of living organisms and are critical for life itself. Various properties of biopolymers differentiate them from small molecules. Biopolymers are macro-polymers and have much larger dimensions compared to small molecules. Biopolymers are made from the four main macromolecules of living organisms: proteins, polysaccharides, nucleic acids, and polyphenol compounds, and they are rich in stereochemistry, conformation, and material complexity. This diversity of composition, structure, and material properties makes natural biopolymers suitable for different life functions such as respiration, energy storage, structural materials, insulation, etc. These materials are integrated into long biological amplitude systems that serve higher levels of biological functions. Biomolecules show high molecular weight, high chain capabilities, complexity, and diversity in stereochemistry and morphology [6, 7].

The increasing concern of producing eco-friendly products that are also biocompatible and biodegradable has led to intensive research on bio-based materials and systems, which would replace conventional plastics. Most of the biodegradable materials used to produce goods are biopolymers or composites synthesized using (partly) biodegradable polymers, e.g., poly (lactic acid) (PLA), poly (butylene succinate) (PBS), or poly (hydroxybutyrate) (PHB) because of their relatively low price. Indeed, such polymers fulfill the requirements for natural biodegradation mainly under aerobic conditions, producing CO₂ and water as residues [8]. Natural biopolymers, including starch, chitosan, and protein-based polymers, lignin, and cellulose can be synthesized in completely eco-friendly processes by physical methods like solvent casting to prepare thin films or spinning to produce fibers. Chemical modifications are also based on natural materials and environmentally acceptable procedures [4].

3 Biopolymer Source

Biopolymers are polymers that are formed from natural sources, either obtained from biological material or biosynthesized by living organisms. Polymers obtained from natural sources, like animals, microorganisms, and plants. Further, biopolymers like polysaccharides, proteins, and polyesters are found in food, personal care, and health maintenance products, either as functional excipients or active ingredients [9]. They possess diverse chemical compositions, molar masses, and physical behavior and occur in complex matrixes of conformation and association. Biopolymers have gained increasing attention due to their plurality of raw materials, natural abundance, and unique properties. In addition, biopolymers exhibit a socioeconomic impact, as they possess a relatively low cost and are renewable, and the current demand for fossil-based materials is not sustainable. Biopolymers have several uses in the food, medicinal, and pharmaceutical sectors. There are documented studies on using biopolymers in diversified sources for food, biomedical, and pharmaceutical applications, including their bioavailability, biocompatibility, bioadhesiveness, or biodegradability.

Biopolymers are active participants in phenomena of great importance to life sciences, such as drug delivery systems, 3D printing, tissue engineering, artificial seeding, artificial organ application, medical textiles, wound dressing, etc. Microencapsulation is mainly used in food industries as a beneficial process that is considered a practical and convenient encapsulating method for protective purposes. The adhesion of isolated films or microcapsules is the next representative inhibitory effect of gas exchange. With the accelerated decline in non-biodegradable polymers, renewable and biodegradable renewable biomaterials are preferred for developing the environmental life cycle. Also, biocatalytic bioprocesses for biotechnological applications form enzymatic catalysis and natural precursor pathways construct supporting undertakings for the bioeconomy based on raw materials from renewable sources [10].

3.1 *Plant-Based Sources*

Biopolymers, as defined here, are macromolecules that are comprised mainly of renewable materials that can be degraded via bio-mechanisms in some form by alkali hydrolysis and/or as monomers without generating toxic products. The sources from which biopolymers are extracted are typically plant-based, but the term biopolymers may also encompass biopolymers that microorganisms or other living organisms have consumed, so also considered is the usefulness of microbial and animal-based sources of biopolymers [11]. Throughout the history of human existence on earth, all materials, whether from renewable or non-renewable resources, are and will be biodegradable when sufficient time is considered. In the past few years, there has been a strong trend toward producing biodegradable packaging materials derived

from renewable resources. This trend is driven by spiraling oil prices, dwindling reserves, environmental issues related to the non-biodegradability of conventional polymers, and the necessity of sustainability. These natural polymers are non-toxic, biodegradable, biocompatible, and can be produced mainly by the casting/solvent evaporation process. These natural polysaccharide biopolymers are also widely used in food packaging.

3.2 *Animal-Based Sources*

Some marine animals also contain fleshy matter that can be converted into other forms, such as biopolymers. Through the processes of extraction, isolation, and manipulation, each animal-based waste provides a distinct kind of biopolymer. Despite all the advantages and disadvantages of potential applications, all the animal biopolymers discussed have a diverse range of bio-applications. The possible applications of non-biomedical products for producing biopolymers were also described to illustrate the flow of circular bioeconomic and zero-waste systems to reduce the losses and pollution of animal waste.

Marine biopolymers, which are specially produced from shrimp and shellfish, are reviewed for their nutritional benefits tied to type 2 diabetic management. Chitosan was observed to inhibit α -amylase and glucosidase enzymes significantly. These constructive results would represent a novel diet therapy for patients with type 2 diabetes in treating and reducing blood sugar accumulation after eating. While there have been many research paper reviews on the production, properties, biodegradability, and use of marine biopolymers from a food processing viewpoint, there does not appear to be comprehensive coverage of the concerns and challenges in regulatory compliance, scalability, and the significant gaps in knowledge or research. Optional solutions and further research are provided from a food processing perspective to understand current constraints better and explore potential ways of utilizing and enhancing marine biopolymers, contributing to scientific research and the industry's sustainable food applications [12].

3.3 *Microbial-Based Sources*

Microbial-derived biopolymers are developing as a vital category of sustainable materials, presenting a possible substitute for petroleum-based synthetic polymers. These biopolymers, synthesized by microorganisms including bacteria, fungus, and algae, are produced under certain environmental circumstances and frequently function as energy stores or structural elements [13]. Examples encompass polyhydroxyalkanoates (PHAs), synthesized by bacteria such as *Cupriavidus necator*, and exopolysaccharides like xanthan gum, produced by *Xanthomonas campestris*. The

microbial materials have various functional properties, which make them suitable for packaging, agriculture, biomedicine, and environmental remediation applications.

The production process for microbial biopolymers often involves fermentation, during which microorganisms are cultivated on sustainable feedstocks like agricultural waste, industrial by-products, or waste streams. This approach reduces waste and diminishes dependence on non-renewable resources [14]. Advancements in metabolic engineering and synthetic biology has markedly improved the efficiency and yield of biopolymer production, allowing customization to satisfy specific performance criteria. Modified bacterial strains can synthesize PHAs with customized features for medical implants, medication delivery systems, or advanced bioplastics. The regenerative bioeconomy, which includes microbial biopolymers, is an innovative concept that supports sustainable development and lessens environmental damage [15]. Environmental remediation initiatives are also investigating the use of microbial biopolymers in wastewater treatment and soil improvement. Bio-based hydrogels from microbial polysaccharides enhance soil water retention and facilitate plant development in dry environments. Microbial polyhydroxybutyrate (PHB), a PHA form, is included in biodegradable mulches and sustainable agricultural films. Ongoing improvements in bioprocessing technology and an increasing focus on eco-friendly alternatives position microbial biopolymers as solutions to critical environmental issues while facilitating a more sustainable future [16].

4 Overview of Biopolymer-Based Composites

Natural polymers' use in food systems signifies a paradigm shift away from traditional petroleum-based products and toward greener substitutes [17]. The food sector has expedited the use of biopolymer technology to satisfy customer preferences and compliance needs as a result of growing worldwide awareness of plastic pollution and evolving regulatory frameworks that limit single-use plastics [18]. These developments not only solve environmental issues but also offer new features that conventional materials are unable to offer [19]. Creating multicomponent systems that blend several biopolymers to provide synergistic effects has been the focus of a recent study [20]. For instance, compared to single-polymer systems, protein-polysaccharide complexes have shown better encapsulation effectiveness for bioactive substances [21]. Due to their structural diversity, biopolymer composites have many uses. They can be made into films, coatings, hydrogels, and nanoparticles, all with specific uses in the food industry. Lipid-biopolymer hybrid nanoparticles have greatly improved targeted delivery systems, enabling the regulated release of nutrients and bioactive substances, especially in dietary contexts [21, 22]. Using active chemicals, nano reinforcement, and cross-linking processes, recent advancements have enhanced these materials' mechanical, barrier, and antibacterial qualities [22, 23].

Biopolymer material technology is considered the newest technique alternative to chemically synthesized preservatives and more effective for fruit coating during postharvest processing and storage. Using biopolymer films as selective barriers

to moisture transfer, oxygen uptake, lipid oxidation, and volatile aroma component losses can enhance food quality and shelf life. Many concepts are used in this technology, as shown in Fig. 1 [24–26]. Biodegradable materials can degrade under temperature, moisture, and oxygen availability without adverse environmental impacts [27]. The edible films and coating technologies can be applied directly onto the different product surfaces to avoid the harmful effects of plastic films; also, it can be eaten directly with food [28, 29]; thus, edible films may be described as thin sheets of edible materials shaped as a coating on surfaces or placed on or between food components [30, 31]. Edible films are obtained from the wastes of several agricultural products and food processing (apple residue, pomace of fruit residues, and vegetable) and byproducts [32].

a. Biodegradable Properties

Biodegradable materials have many properties such as biocompatibility, biodegradability, renewability, edibility, non-toxicity, non-polluting, low cost [33–39], also considered a good film-forming for fruit and vegetables and have many desirable physicochemical characteristics [40, 41]. Many studies have proved that edible films and coatings have several advantages and functions when applied to the surfaces of different products (Table 1).

Numerous factors influence the different properties (mechanical, optical, and barrier effects against gases) of the edible films, including polymer sources and their concentration, chemical structure, plasticizer type, component concentrations, degree of polymerization, and film drying temperature [56]. Many studies presented

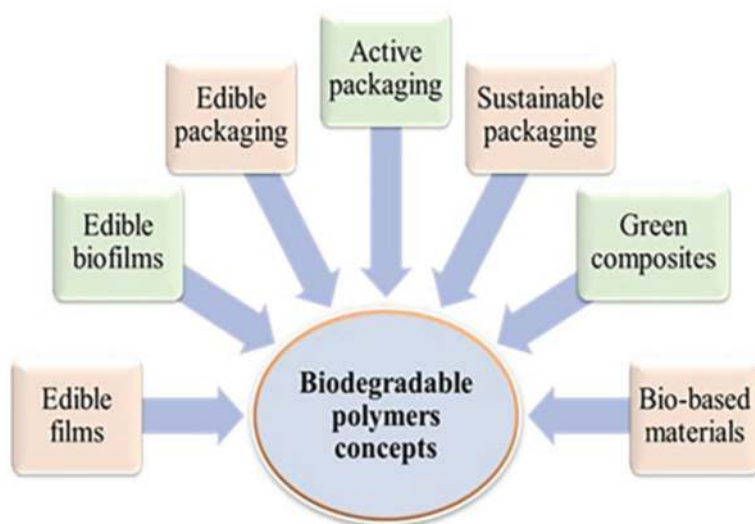


Fig. 1 Biopolymers concepts

Table 1 Advantages and functions of biodegradables

Advantages and functions of edible films	References
Minimize the adverse environmental effects of non-biodegradable petroleum-derived packaging materials	[42]
Limit the moisture migration; reduce lipid migration	[43, 44]
Reduce deterioration, mitigate food deterioration, and extend the storage period of agricultural products	[45, 46]
Minimize fruits' respiration rate, weight loss, and oxidation reaction rates during storage	[47]
Improve the safety, appearance, and stability of fresh food	[48, 49]
Barrier materials for gas diffusion (water vapor, CO ₂ , and O ₂); also, barrier for light	[50, 51]
A barrier to control the transfer of lipids, moisture, and flavors	[52]
Barrier materials to minimize oil absorption in fried foods	[53]
Preservatives and bioactive compounds (nutrients, vitamins, antibrowning agents, antioxidants, antimicrobials, and flavoring) are carriers for food products to delay discoloration and bacterial growth	[33, 54, 55]

the various advantages of biodegradable films in different food processing and packaging (fresh-cut fruit, vegetables, and processed meats) and noted that the edible films and coatings are considered to be the technology that prioritizes safety while being environmentally friendly and quality of agricultural products, due to their biodegradability [30, 33].

b. Biodegradable Classification

Generally, the biodegradable polymers extracted from natural renewable resources which classified into three types; polysaccharides (pectin, starch, cellulose, and chitosan), proteins (casein, whey, wheat, soy protein, zein, and gluten), and lipids (oils, waxes, fatty acids, and mineral oils), or their combinations [57, 58] as shown in Fig. 2.

These natural biodegradable polymers have received a lot of attention in recent years, because to their inherent environmental benefits and varied functional features. Polysaccharides have great film-forming properties and good oxygen barriers, but they often have low moisture resistance due to their hydrophilic nature. Protein-based polymers have remarkable mechanical strength and barrier qualities against oxygen and carbon dioxide, while also allowing for active functionality via reactive side chains that can bind bioactive chemicals. Lipid-based materials work well as moisture barriers, although they generally lack structural stability when employed alone. To address these individual constraints, researchers have created complex composite systems that carefully mix different biopolymers to produce synergistic materials with increased functionality. For example, protein–polysaccharide complexes use electrostatic interactions and hydrogen bonding to form more stable networks with

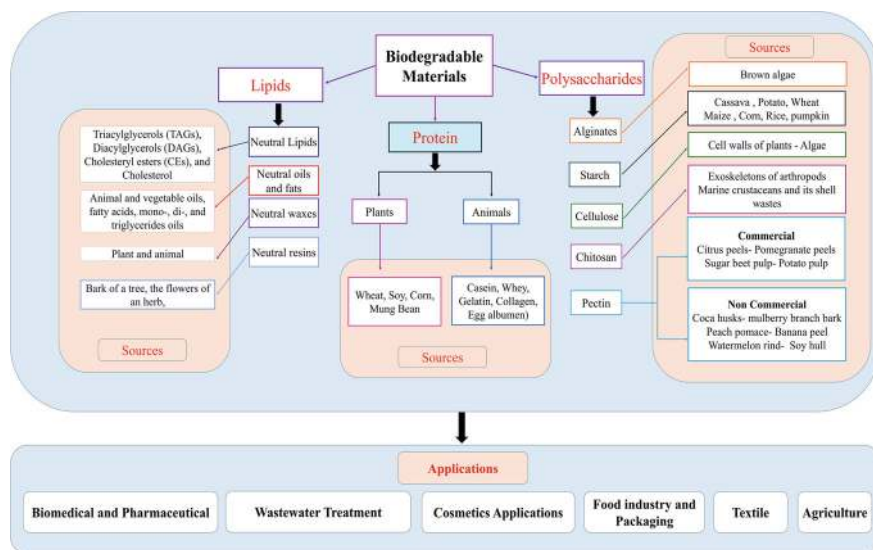


Fig. 2 Classification and applications of biodegradable polymers

improved mechanical properties and lower water sensitivity, whereas lipid incorporation into hydrophilic matrices results in emulsion-based films with significantly improved moisture barrier properties. These novel combinations have enabled the creation of biodegradable packaging materials that progressively outperform traditional plastics while providing greater environmental advantages through full biodegradation in natural settings.

1. Polysaccharide

Carbohydrates are recognized as valuable biopolymers and emerge as promising alternatives to plastic materials in food packaging. They encompass a range of structures, including monosaccharides, disaccharides, oligosaccharides, and polysaccharides [59]. Polysaccharide polymer is recognized as the main energy source in human diets, owing to its capacity to create films and gels through variations in pH or temperature [60, 61]. Polysaccharides comprise long chains of monosaccharide units linked by glycosidic bonds and are considered important biopolymers in developing biodegradable packaging materials. They can be classified as non-polyelectrolytes or polyelectrolytes, which are further subdivided into positively and negatively charged substances [40, 62, 63]. Costa et al. [62] observed that the polysaccharide polymers exhibited distinct physical, optical, and chemical properties compared to other polymers, as the electrostatic interactions within the polyelectrolyte complex were more significant than most secondary binding interactions. The edible polysaccharide coatings also demonstrated effective coating-forming abilities and low oxygen permeability characteristics [61]. Azman, Khairul [58] states that films made of polysaccharides are strong, malleable, see-through, and gas barrier effective because

of their linear structure. Their main problem, though, is that they are hydrophilic, which means they don't do a good job of acting as a water vapor barrier.

Chitosan (CH): Chitosan is a promising natural linear cationic and heteropolysaccharide. Chitosan polymer comes by the partial deacetylation of chitin, the degree of deacetylation ranging from 40 to 98%, the higher deacetylation of chitosan makes it soluble in acidic solution and can't soluble in water solution [64]. The different properties of chitosan polymer (chemical, physical, antimicrobial and antibiofilm properties) rely on molecular weight, deacetylation, and crystallinity degree, the extent of ionization/free amino group [65, 66]. Chitosan is a promising natural linear cationic and heteropolysaccharide comprising mainly units of β -(1-4) glycosidic bonds linked by 2- amino- 2-deoxy -D- glucopyranose and traces of 2-acetamide-2-deoxy-D-glucopyranose monomers linked by β -1,4glychitosanidic bond where it can obtain from alkaline deacetylation and enzymatic degradation of chitin [66, 67], also considered a second most abundant biosynthesized polymer in nature (after cellulose) and next to lignin [68, 69]. Chitosan obtained from exoskeletons of arthropods such as; fungal cell walls and, insects [70–72], marine crustaceans and their shell wastes such as shrimp [73], lobsters [74], krill [66], crayfish and crabs [73, 75]. It possesses antibacterial, surface modification, biocompatibility, non-toxicity, and simple film ability [71]. The Food and Drug Administration (FDA) of the United States authorized chitosan as GRAS (Generally Recognized as Safe) and includes safety characteristics: it is non-toxic, biodegradable, economically priced, and exhibits superior film-forming properties [76]. Consequently, it is extensively utilized in the medical and food industries, chemical manufacturing, and other areas, as observed in Fig. 2. The antibacterial efficacy of chitosan is contingent upon its degree of deacetylation and concentration [72].

Chitosan has an essential place in polysaccharides and is widely found in nature and demonstrated excellent biological properties, in addition to it has several advantages like biocompatibility and availability [71], biodegradability [77], low cost, and environmentally friendly [41, 78], non-toxicity [79], ideal biopolymers film-forming ability [80]; also presenting functional properties and bioactivity, such as antimicrobial properties for the foods during storage.

Starch: Starch is a polysaccharide that can be obtained in many plant organs, such as the endosperm, roots, tubers, and immature fruits. It has worldwide applications in various industries [81]. The films made from cassava starch show better barrier properties, biodegradability, and transparency. Moreover, these films are flexible, colorless, odorless, tasteless, non-toxic, and economical. These films are also more effective than potato, wheat, and maize starch films in lowering water permeability due to their lower lipid and protein content within the granules. According to Rahmadi Putri, Adhitasari [82] the composition of cassava starch might be broken down into two components: amylopectin, which has a molecular weight of 0.7×10^8 , and amylose, which has a molecular weight of 1.03×10^6 , which indicates a partly crystalline and granular structure. Sweet potato starch has higher amylose content than yam, cassava, and plantain starch. Starches high in amylose have films which provide better elongation but poor mechanical properties [83]. Compared to cassava,

rice, or potato starch, corn starch has much lower hygroscopic nature. It generally consists of 75% branched amylopectin and 25% linear amylose. Maize starch is made up of 84.07% carbohydrates, 2.76% proteins, 0.85% fiber, 1.97% ash, and 3.02% fat.; cornstarch films have satisfactorily functioned as oxygen-resistant coverings for fish steaks [84].

Cellulose: The leading type of polymer obtained from plants is cellulose. Cellulose is remarkably flexible, biodegradable, and gas permeable, making it exceptional for food packaging. It is a linear polymer composed of glucose joined through β -1,4 glycosidic bonds, resulting in extended chains. These chains are held together by intermolecular and intramolecular hydrogen bonding, which creates planar sheets. These sheets then interact with each other through van der Waals forces and improve the cellulose crystalline structure's stability, thus compromising cellulose's durability for a more soluble fiber. Cellulose polymer and its notable complexity are insoluble in water and given solvents [76, 85, 86]. After dissolving, the cellulose can be processed into films with advantageous properties. The multitude of active hydroxyl groups in the chain allows for many chemical processes such as cross-linking, etherification, and oxidation, simplifying the incorporation of additional supplements to cellulose films. Out of all the modifications, antimicrobial functionalization is highly crucial for enhancing the properties of the cellulose films. In contrast to specific natural polymers like chitosan that exhibit intrinsic bactericidal capabilities, cellulose does not contain these characteristics, restricting its use [87, 88].

Pectin: Pectin is anionic polysaccharide predominately made of neutral sugars and α -(1–4) D-galacturonic acid linkages that are partially esterified with methyl or acetic acid [89, 90]. Research has shown that pectin is one of the most prevalent polysaccharides in all plant tissues' middle lamella and primary cell walls [91, 92]. Pectin can be segregated into two divisions based on esterification degree (ED): Low-methoxyl pectin with an ED lower than 50% and high-methoxyl pectin with an ED higher than 50%. Pectin's degree of methyl-esterification can be assessed by the amount of methanol reacted per 100 mol of galacturonic acid or by the amount of pectin's carboxylic groups transformed to methyl esters [90]. The degree of esterification is one of the most important factors of low- and high-methoxyl pectins since it determines their biochemical and physicochemical properties and many applications due to their specific nature [37, 93]. For pectin, various extraction processes include microwave, subcritical water, ultrasound, and enzyme-assisted extraction [90, 94].

Several studies show that pectin stands out as an edible film and biocomposite material for food packaging [95, 96]. Methoxyl groups in the pectin structure increase its value due to their hydrophobic characteristics, making it useful across various food products. These applications include, but are not limited to, use as an emulsifier, stabilizer, and thickener, and as a gelling ingredient in beverages such as fruity milk drinks, yogurt, ice cream, and jams [59, 92, 97].

Alginates: Alginates are structural polysaccharides made from brown algae that alternately contain blocks of mannuronic acid and glucuronic acid residues. Under specific pH levels, soluble particles form synergistic gels with pectin in these ionic linear

copolymers known as polyuronates [98–100]. Alginates are natural colloidal polysaccharides characterized by their water solubility, biodegradability, non-toxicity, and non-irritating properties. These primarily originate from diverse varieties of brown seaweed. Bacterial alginates are derived from specific species of *Pseudomonas* and *Azotobacter*. Due to monosaccharide sequencing and enzymatically controlled reactions, alginates are used for various biological and medical applications [101, 102]. Alginate-based edible films and coatings are increasingly recognized for their ability to enhance quality and extend the shelf life of various food products, including fruits, vegetables, meat, poultry, seafood, and cheese by regulating respiration and improving product quality [103].

2. Protein

Protein can be found in many different foods and plants. Some examples include seafood, soy, wheat gluten, corn zein, corn, sodium caseinate, gelatin, peanuts, collagen, pumpkin seeds, lentils, rice, sesame seeds, egg white protein, and rice protein. These proteins have been employed in the production of films and coatings [104]. Protein-based polymers have recently attracted interest due to their superior film-forming properties. Protein-based films have more advantages than polysaccharide and lipid films due to their enhanced gas barrier properties, oxygen (O₂), carbon dioxide (CO₂), nitrogen (N₂), and odors [58]. Khin, Ahammed [104] reported that edible films and coatings derived from proteins can be categorized into two primary groups: plant-based and animal-based, based on their source of origin. Protein properties, such as molecular weight, solubility, and isoelectric point (IP), are essential for fabricating films and coatings.

Two major milk proteins often used in filmmaking are whey and casein. These proteins are used to make films that are transparent and tasteless. The casein films treated with calcium hydroxide exhibit enhanced barrier characteristics and increased rigidity due to improved protein–protein cross-linking facilitated by calcium, while casein films treated with sodium hydroxide have better optical and tensile strength properties, but whey protein isolate (WPI) is the most common biomaterial used to make films due to its high protein content and excellent oxygen barrier properties at low to intermediate relative humidity levels [105]. A dairy industry by-product known as whey protein has recently attracted much attention, accessible as whey protein concentrates and whey protein isolates, containing between 20% and over 90% protein, respectively. They have been noted to exhibit superior mechanical and barrier characteristics, as examined by multiple researchers. In addition to being transparent and flexible, whey protein films are highly effective at blocking the passage of water, gas, smell, and oil. Also, whey protein forms a stronger and more cohesive film than native proteins when subjected to heat [98]. The structural protein collagen is present in all connective tissues, including skin, bones, and tendons; they make up around a third of all proteins found in mammals. Meat products often use films made of collagen to keep them wet and consistent in appearance. In addition to improving the cooking time of meat products when heated [105].

Gelatin, a protein derived from byproducts of the meat industry, is utilized to produce resilient films containing 20–30% gelatin protein and 10–30% plasticizer.

The thickness and mechanical qualities of edible gelatin films are enhanced by increased protein content, whereas water vapor permeability (WVP) diminishes. Moreover, films derived from gelatin exhibit subpar water vapor barrier characteristics compared to other proteins, limiting their use. Gelatin is a colorless, tasteless, water-soluble protein derived from the partial or complete hydrolysis of collagen, characterized by its low cost and high availability [106].

3. Lipids

Lipid compounds include many types of substances, such as neutral lipids, natural oils and fats (animal and vegetable oils, fatty acids, mono-, di-, and triglycerides, and hydrogenated or transesterified oils), natural waxes (of plant and animal origin), natural resins, essential oils, licorices, emulsifying agents, and surfactants [107]. Lipid compounds can serve as moisture barriers in film packaging; however, there are issues with organoleptic and textural attributes. In addition, lipid-based films are usually opaque and rather stiff. Still, incorporating lipids with polysaccharide- or protein-based films improves the water barrier property of the packaging films because of their hydrophobic nature. The most common lipid compounds to formulate the films are waxes, triglycerides, and resins [58, 108]. Lipid substances are incorporated into edible films to enhance flexibility, hydrophobicity, and cohesiveness. It serves as a moisture barrier and, in some cases, an oxygen barrier, which allows for maintaining food quality for long periods. Lipid-based edible films have potential uses in confectionery, fruits, vegetables, dairy, chocolate, cereal, poultry, fish, frozen, and dried products [107].

Lipids, especially those which are hydrophobic or capable of impeding water vapor transfer, have been widely appreciated in the food industry. The resistance of lipid molecules to gas and vapor transport stems primarily from their hydrophobic nature and their structural resistance. Therefore, lipids offer new ways of using non-traditional, sustainable, and renewable raw materials for food packaging due to their superior antioxidant, antibacterial properties, and other physicochemical qualities [109].

5 Processing Methods and Techniques of Biodegradable Materials

Types of biomaterials, additives (such as nanoparticles), food, storage conditions, and preparation methods are only a few of the variables that might impact the final product's quality in bio-nanocomposites. There are different ways to prepare edible films, such as the casting method, molding method, layer-by-layer method, and extrusion method [56, 95]. Casting, electrospinning, melt mixing (extrusion), and polymerization are some of the most typical methods used to create polymeric bio-nanocomposites. The casting's relative ease of use has piqued scientists' curiosity more than competing methods. The extrusion procedures were more commercial than other approaches in the same area [110]. Ahari, Golestan [110] showed that

casting is a popular, easy, and cheap method scientists use in the lab. You won't need any fancy tools or spaces to use this method. Casting is a four-step process. First, the polymeric solution is made, then put into the mold, and allowed to dry; finally, post-processing is done to strengthen the structure. Melt blending, also known as melt mixing, is a high-tech alternative to the traditional casting procedure used in commercially available films. It is a continuous manufacturing system. This method uses a lot more energy than the solvent casting method, but it produces a lot more films every hour. The polymerization process is more extensive and complex than other methods since it involves a reaction (the interaction of monomers and photoinitiators). However, this method has demonstrated promise in enhancing the properties of polymeric films [111].

6 Novel Reinforcement of Biopolymer Materials

Many studies have proven that blending, cross-linking, and using nanocomposites can overcome the drawbacks of the different films formed from a single component to improve the films' functions and properties (physical, mechanical, barrier, thermal, and antimicrobial) [31, 50, 112] as shown in Table 2. Individual biodegradable films frequently do not possess adequate qualities, combining them with additional materials improves their performance as smart film packaging [113]. Nanomaterials, cross-linkers, bioactive chemicals, and other polymers can be added to biopolymers to improve and modify their mechanical resistance and hydrophilicity [110].

a. Polysaccharide-Based Composites

Starch can be combined with different polymers such as chitosan, gelatin, casein, gums, proteins, carrageenan, or poly(vinyl alcohol) (PVA); also, the pectin polymer can be incorporated with chitosan, papaya puree-based films, and essential oil nanoemulsions to improve the properties of the different films [114, 115]. Several studies have shown that essential oils, including cinnamaldehyde, clove bud, orange oil, and Mexican lime, can enhance their qualities with pectin films, integrating active compounds like essential oils of basil and thyme, such as ascorbic acid, tocopherol, ferulic acid, and tannic acid, can improve the properties of chitosan films [116].

The utilization of pure chitosan is constrained by inadequate mechanical characteristics and insufficient water resistance. To surmount these challenges, blending frequently incorporates other biopolymers (such as pectin, gelatin, zein, cellulose, etc.) into chitosan films [76].

b. Protein–Polysaccharide Complex Nanoparticles

Because of their complementary functional characteristics, protein–polysaccharide complex nanoparticles are among the most promising biopolymer-based delivery systems. Although hydrogen bonding and hydrophobic contacts also aid in stability, these complexes are typically established through electrostatic interactions between

Table 2 Mechanical, opacity, and water vapor permeability (WVP) properties for the different composite films

Composite films	Plasticizer	Mechanical properties			Water Vapor Permeability (WVP)		Opacity (mm ⁻¹)	References
		Tensile strength, (MPa)	Young's modulus (MPa)	Elongation at break (%)	WVP value	Unit		
SP/Gly	Gly	2	19	–	–		–	[117]
SP/HPS	HPS	6.71	140	–	–		–	
SP/HPS/TA	HPS/TA	9.79	170	–	–		–	
SA _{3%} /CC _{0.1%}	Gly _{0.8%}	–	–	–	2.42×10^{-13}	g · m ⁻¹ · s ⁻¹ · Pa ⁻¹	–	[83]
SA _{5%} /CC _{0.05%}	Gly _{1.2%}	–	–	–	5.13×10^{-13}		–	
Neat PLA	–	56.2	1200	7	1.1×10^{-13}	kg · m ⁻¹ · s ⁻¹ · Pa ⁻¹	–	[111]
PLA/NPG	–	37.5	1060	110	1.85×10^{-13}		–	
LMP _{1%} - NPG-PLA	–	33	950	236	0.95×10^{-13}		–	
CP	Gly	6	–	58	11×10^{-9}	g · m ⁻¹ · s ⁻¹ · Pa ⁻¹	–	[72]
CP-CUR _{50mg}		6	–	79	9×10^{-9}		–	
CP-CUR _{150mg}		14	–	56	8×10^{-9}		–	
PE	Gly	9.35	13.10	62.63	4.11×10^{-12}	g · cm ⁻¹ · s ⁻¹ · Pa ⁻¹	0.54	[118]
PE/fiber		10.76	16.38	65.53	4.03×10^{-12}		0.88	
PE	Gly	62	1467	20	7.3×10^{10}	g · mm · h ⁻¹ · cm ⁻¹ · Pa ⁻¹	3.4	[98]

(continued)

Table 2 (continued)

Composite films	Plasticizer	Mechanical properties			Water Vapor Permeability (WVP)		Opacity (mm ⁻¹)	References
		Tensile strength, (MPa)	Young's modulus (MPa)	Elongation at break (%)	WVP value	Unit		
WP /PE		13	352	16	9.6×10^{10}		3.0	
PE	–	1.36	–	–	0.035	g.mm.m ⁻² .h ⁻¹ .Pa ⁻¹	–	[45]
PE/ Corn flour	–	7.47	–	–	0.008		–	
PE/ Beetroot	–	3.79	–	–	0.011		–	
PE	Tween 80	2.09	713	23.56	9.96×10^{-7}	g.m ⁻¹ .h ⁻¹ .Pa ⁻¹	–	[63]
PE/Pe		8.18	719	19.47	1.19×10^{-7}		–	
PE/NE		1.33	623	21.11	4.27×10^{-7}		–	
PE	Gly	14.78	2.32	6.37	13.22×10^{-11}	g.m ⁻¹ .s ⁻¹ .Pa ⁻¹	0.75	[25]
PE/CEO _{1.5%}		33.78	2.87	11.75	6.52×10^{-11}		3.15	
Neat PVA	–	35.42	225.45	273.70	8.11×10^{-9}	g.m ⁻¹ .s ⁻¹ .Pa ⁻¹	–	[119]
PVA/CD/MOF _{4%}	–	41.95	174.78	381.65	6.76×10^{-9}		–	
GEL	Gly	32.5	–	17	4×10^{-10}	g.m ⁻¹ .s ⁻¹ .Pa ⁻¹	–	[120]

(continued)

Table 2 (continued)

Composite films	Plasticizer	Mechanical properties			Water Vapor Permeability (WVP)		Opacity (mm ⁻¹)	References
		Tensile strength, (MPa)	Young's modulus (MPa)	Elongation at break (%)	WVP value	Unit		
SA-GEL		46	–	26.5	2.73×10^{-10}		–	
SA		39	–	15	4.37×10^{-10}		–	
Keratin/CNC(1:1)	–	1.45	–	78	1.3	mg.mm.h ⁻¹ .Pa ⁻¹ .m ⁻²	–	[121]
Keratin/CNC(4:1)	–	2.5	–	20	1.05		–	
Keratin/CNC(1:4)	–	0.45	–	25	1.3		–	
Keratin/CNC-CA(1:1)	–	2	–	135	0.95		–	
Keratin/CNC-CA(4:1)	–	6.35	–	30	0.6		–	
Keratin/CNC-CA(1:4)	–	1.5	–	74	0.9		–	

Soy protein (SP), Hyperbranched polysiloxanes (HPS), Tannin acid (TA), Starch (SA), Calcium carbonate (CC), Glycerol (Gly), Lignin microparticles (LMP), Poly(lactic acid) (PLA), Ethylene–vinyl acetate–glycidyl methacrylate (NPG), Chitosan/polyvinyl alcohol (CP), Curcumin(CUR), Pectin (PE), Whey protein (WP), Pickering emulsion (Pe), Nanoemulsion (NE), Clove bud essential oil (CEO). Poly (vinyl alcohol) (PVA) carbon quantum dots-loaded metal–organic frameworks (CD/MOF), Sodium alginate (SA), Gelatin (GEL), Cellulose Nanocrystals (CNC), Citric acid-modified Cellulose Nanocrystals (CNC- CA)

polysaccharides and proteins with opposing charges. Whey protein–pectin, soy protein–chitosan, and gelatin–alginate complexes are only a few of the protein–polysaccharide combinations discovered recently; each has unique benefits for particular bioactive substances [122].

The creation of layer-by-layer constructed nanoparticles, in which alternating layers of proteins and polysaccharides produce nanostructures with precisely regulated characteristics, has been a noteworthy accomplishment in this sector [123]. While maintaining regulated release profiles, these multilayered systems have shown improved protection for sensitive bioactive against environmental stresses [124]. For instance, beta-lactoglobulin–carrageenan complexes extended the stability of vitamin D in fortified dairy products by shielding it from heat processing and UV deterioration [125].

The rational design of these complex systems is now made easier by advances in characterization techniques, such as sophisticated microscopy and spectroscopic approaches, which have improved knowledge of protein–polysaccharide interactions at the molecular level. In addition, computer modeling techniques have reduced development time and experimental testing requirements by predicting stability and release kinetics under different conditions [126].

c. Lipid–Biopolymer Hybrid Systems

To get around the drawbacks of single-component systems, lipid–biopolymer hybrid systems combine the benefits of biopolymer matrices with lipid-based carriers (such liposomes, solid lipid nanoparticles, and nanoemulsions). These hybrid structures, which are often composed of a biopolymer shell encircling a lipid core, provide a flexible delivery system for bioactive substances that are both hydrophilic and hydrophobic [127]. To improve stability during food processing and storage, recent advancements have concentrated on optimizing these systems' interfacial characteristics [126].

Substantial strides have been made in developing lipid–protein hybrid nanoparticles with enhanced functional characteristics. The remarkable acidity stability of casein-coated nanoemulsions makes them ideal vehicles for delivering lipophilic nutrients in dairy products and drinks [128]. Likewise, zein–phospholipid hybrid particles have demonstrated the potential for encasing essential oils, offering antibacterial properties while concealing unwanted tastes [129, 130]. Recent research has also investigated the potential of stimuli-responsive lipid–biopolymer systems that react to particular environmental triggers in the gastrointestinal tract. By allowing the site-specific release of bioactive chemicals, these intelligent delivery systems maximize their biological benefits while reducing degradation during transportation [131]. To improve the survival and efficacy of probiotics, pH-responsive chitosan-coated liposomes have been created for targeted colon distribution [132].

d. Fillers and Fibers

Calcium carbonate improves physical qualities when utilized as a filler in biodegradable films. Films made from chitosan and calcium carbonate demonstrate enhanced barrier qualities against oxygen, carbon dioxide, and water vapor, while exhibiting

decreased hydrophilic capacity. In a similar manner, *in situ* modified CaCO_3 -chitosan composite coatings have improved oxygen barrier properties and antibacterial efficacy [83]. Recent studies have demonstrated that the integration of natural fibers into edible film matrices enhances many film characteristics. Natural fibers can be classified as either vegetable (cellulose) or animal (protein) fibers. Natural fibers, when subjected to alkali treatment, provide notable advantages such as enhanced thermal stability, decreased moisture absorption, and augmented crystallite size in the resultant materials [133–135]. The incorporation of nanofillers into chitosan matrices effectively mitigates shortcomings including inadequate mechanical and barrier characteristics, limited thermal stability, and suboptimal transparency [56].

7 Technology-Assisted Delivery Systems

The use of nutraceuticals, bioactive chemicals, and functional additives in food items has been transformed by delivery systems enabled by nanotechnology [136]. These devices offer previously unheard-of control over physicochemical characteristics and interactions with food matrices since they function at the nanoscale (1–100 nm) [137, 138]. The development of biopolymer-based nanocarriers, which provide benefits such as increased solubility, better stability, controlled release, and targeted distribution of bioactive components, has been the focus of recent advancements [139].

Several manufacturing methods have surfaced, including electrospinning, nanoprecipitation, and microfluidic approaches, each with unique benefits for certain uses [140]. For example, zein and gelatin-based electrospun nanofibers have shown remarkable polyphenol encapsulation efficiency while preserving their antioxidant activity during food processing and storage [141]. In addition, thanks to innovations in green synthesis, the production of nanoparticles is now less harmful to the environment, which aligns with the food sector's sustainable development goals [142].

One noteworthy advance in recent years has been the creation of multifunctional delivery methods that concurrently address several issues, including targeted release in the gastrointestinal tract, improved bioavailability, and protection against degradation. In order to provide intelligent release mechanisms that maximize bioactive efficacy, these complex systems frequently incorporate sensory responses to environmental cues like as pH, temperature, and enzyme activity [143].

8 Microencapsulation of Bioactive Compounds

Encapsulating bioactive compounds in carriers based on biopolymers has made great strides, solving important problems with food applications such as stability, bioavailability, and sensory impact. The encapsulation of novel bioactive including prebiotics,

probiotics, enzymes, and bioactive peptides has been the subject of a recent study that goes beyond conventional vitamins and antioxidants [144]. While preserving their functioning during processing, storage, and digesting, these systems shield delicate substances from deterioration [145]. New encapsulating technologies were created, such as biomimetic mineralization techniques, supercritical fluid-based methods, and precision spray-drying using biopolymer matrices [146]. For certain bioactives and intended uses, each approach has unique benefits. For example, Curcumin electro-spray in a gelatin–alginate matrix with supercritical CO₂ assistance achieved about 95% encapsulation efficiency while maintaining antioxidant activity throughout shelf life in model food systems [147].

9 Smart Packaging Systems

Environmentally friendly, biodegradable, and biocompatible packaging materials made from renewable resources have piqued the interest of academics and consumers in the creation of multipurpose and adaptable packaging materials. New packaging materials not only make food last longer (active packaging), but they also give customers real-time feedback on whether their food is fresh or spoilt (smart packaging) [110]. Packaging systems are essential for maintaining food quality and minimizing food waste. The food industry depends on plastic film packaging due to its flexibility, lightweight nature, and cost efficiency. But its inert nature causes problems for the environment; thus, we need to find alternatives made of biodegradable polymers. However, the mechanical, thermal, and moisture barrier characteristics of biodegradable polymers are inadequate for use in food film packaging. The film packaging lacks accurate information about the freshness of meat, prompting the development of smart film packaging with biosensors, enabling efficient real-time monitoring of food quality while offering a biodegradable alternative [58, 113].

The innovations of smart packaging, such as active and intelligent, have improved the marketing of food products whether simultaneously increasing storage time through passive protection from external factors and contamination. Chemicals that have been refined or altered to increase the food's shelf life, make it safer to eat or improve its sensory qualities are known as active packaging materials [148].

a. Active Packaging Application

Active packaging is systems that incorporate antimicrobials, nanomaterials, antioxidants, and other gas and moisture absorbers, which enhance the qualities of packaging films and extend the shelf life of food goods [110]. Antimicrobial packaging is an advanced technology that protects perishable goods from harmful microbes such as bacteria, viruses, and parasites. Nanoencapsulation and nanocarriers loaded with natural antimicrobials have improved the performance and effectiveness of active food packaging [148].

The advancement of active packaging has been propelled by rising customer demand for minimally processed goods that offer prolonged shelf life and improved

safety characteristics. These systems utilize many creative processes, including the regulated release of active chemicals, the absorption of unwanted contaminants, and the establishment of changed atmospheres inside the packaging environment. Multilayer active packaging films that integrate natural antimicrobial agents like nisin, natamycin, and plant extracts are particularly promising, as they are deliberately embedded inside polymer matrices to enhance their movement kinetics into the food matrix. Moreover, oxygen scavengers using iron powder, ascorbic acid, or enzymatic systems have been successfully included into packing materials to avert oxidative degradation of delicate food constituents. The synergistic integration of various active ingredients in a single packaging system has demonstrated exceptional efficacy in simultaneously combating multiple spoilage mechanisms, thereby considerably prolonging product freshness while preserving nutritional quality and sensory attributes throughout the distribution chain.

b. Intelligent (Responsive) Packaging

Intelligent (responsive) packaging is smart responsive packages which are identified as biosensor-assisted systems that interact with the food packaging by actively responding to both the features of the food and the state of the food container. Such technology allows the control of the state of food or the surrounding factors in real location and in real time [113]. Active food sterilization systems capable of responding to different factors may include nanomaterials, chemical substances capable of absorbing and reacting with oxygen, ethylene, and food flavor.

All these materials and devices, which in one form or another influence the environment and the food pack without contact, encapsulate the basic concept of active packaging materials. These devices not only assist to mitigate food waste but contributed in improving health and safety. Oxygen scavengers remove leftover oxygen within food packaging or improve its barrier qualities against this gas. At the same time, moisture absorbers regulate humidity levels within food packaging, but ethylene scavengers postpone the ripening process, prolonging shelf life [85, 113, 148].

The food packaging sector has developed intelligent packaging technologies to improve food safety and quality throughout the supply chain, providing valuable insights through ongoing monitoring. Packaging incorporates active components such as essential oils, metal-based nanoparticles, natural clay, carbon quantum dots (CDs), and plant extracts to maintain food quality. Numerous natural colors, such as anthocyanins, carotenoids, and chlorophylls, are indicators for detecting alterations in pH, microbial metabolites, ammonia concentrations, and compounds linked to rotting [119]. Huang, Li [72] reported that Nanotechnology has revolutionized the packaging industry by making materials more long-lasting, practical, and efficient. Innovative new avenues for creating high-tech packaging have been revealed by nanoparticles, particularly metal-organic frameworks (MOFs) and carbon quantum dots (CDs). Carbon quantum dots' photoluminescence, tissue compatibility, and low toxicity have made them a potential material well-suited for biological and food packaging applications because of their antioxidant, UV-blocking, and antibacterial

characteristics. Their use in food packaging is further enhanced by their capacity to detect ammonia and pH levels.

Intelligent packaging materials can detect germs and food deterioration, increase food safety and quality, improve shelf life, alert consumers to potential problems, and provide information [110, 148]. Notwithstanding progress in creating dual-function packaging solutions that serve preservation and monitoring functions, most research has focused solely on singular (active or intelligent) functions. Furthermore, investigations into dual-functional packaging materials are confined to incorporating active compounds and natural pigments (anthocyanins). Nevertheless, numerous natural pigments necessitate enhancement in specific areas due to their possible interactions with food components and vulnerability to degradation from environmental factors such as hydration, ultraviolet light exposure, oxidation, temperature variations, and enzymatic activity. Resolving these difficulties necessitates the creation of effective freshness monitors possessing antioxidant and antibacterial characteristics [119, 149, 150].

c. Intelligent Packaging Applications

Intelligent packaging systems equipped with smart indicators respond to alterations in the packaging environment and deliver real-time information to the user about the freshness and spoilage of the packaged product [110].

Otero-Herrera, Fuentes-Gaviria [83] showed that the edible coating made of starch and calcium carbonate with glycerol as a plasticizer was evaluated for the confections. The material utilized for the candy wrapper displayed minimal WVP, and it preserved the sensory characteristics of the candy over 21 days. The organoleptic attributes of the confections (color, flavor, and texture) received the highest marks, whereas the examiners deemed the aroma satisfactory. The scores remained steady and improved with storage time, showing that the confections did not change their sensory properties. This suggests that these films could be used in confectionery packaging because they retained their physical integrity throughout storage. In contrast, the tasters swallowed candy wrappers and were willing to digest them. Hong, Riahi [119] found that there was encouraging potential for enhancing and tracking shrimp freshness with the developed PVA-based multifunctional smart packaging films, which included (CD/MOF) carbon quantum dots-loaded metal-organic frameworks. These novel composite coatings exhibited exceptional UV protection and powerful antioxidant and antibacterial properties. Also, it stopped the pH from rising, the growth of microbes, the oxidation of stored shrimp, and weight loss. A dependable visual predictor of changes in shrimp quality over time was the color shift of PVA/CD/MOF film following ammonia exposure. An interactive effect between CD and MOF offers varied capabilities for smart packaging applications, suggesting that incorporating CD into MOF (CD/MOF) is a promising strategy. Huang, Li [72] indicated that the pork pH varied between 5.8 and 6.2, qualifying it as fresh; they stored the pork without packaging and coating it with CP-Cur and found that the pork pH was 6.06 on day 0. Following three days of storage, the pH levels of unwrapped pork and pork coated with CP-Cur0 were 6.65 and 6.43, respectively, indicating

spoilage of the pork. On day 5, the pH of the CP-Cur150 film group was 6.23, indicating the onset of deterioration in the pork. On day 7, the pork pH elevated in all treatment groups, although it remained considerably lower in the CP-Cur150 film group compared to the other groups. To assess antibacterial efficacy, they compared unwrapped pork with pork encased in CP and CP-Cur at varying concentrations. The initial bacterial colony count for the untreated pork was approximately 5.45 Log₁₀ CFU/mL; after one day of storage, results indicated minimal bacterial survival in the CP-Cur150 film-packed pork. This suggests that the CP-Cur150 film is suitable for food packaging, namely, to prolong the shelf life of pork. For the shrimp's freshness, the CP-Cur0 film didn't show any visible changes while it was in storage, so it wasn't a good indicator. However, by combining it with the CP film, it was able to track any changes in pH levels while the shrimp were in storage. A shrimp that has a light yellow or yellow film on it is considered fresh; however, a shrimp that has a red film on it is considered spoiled and should not be eaten.

The impact of pectin combined with corn flour and beetroot as a coating on tomato fruits has been examined by Sucheta et al. [151], which investigates the impact of a coating comprising pectin, corn flour, and beetroot on tomato fruits and determined that the optimal coating was pectin/corn flour. The combination reduced the percentage of weight loss, delayed the rate of respiration, and maintained internal quality during the 30-day storage period. Added time to tomatoes' storage life and showed very little shrinkage when put away. Latiff, Shaik [113] stated that smart packaging using natural colorants and nanoparticles provides a viable solution for preserving meat freshness by facilitating real-time monitoring of spoiling and alerting consumers to different changes in the packaging environment. By employing an edible coating consisting of guar gum/chitosan and 1% citronellal/hydroxypropyl- β -cyclodextrin, the storage stability of Harbin red sausage at 4 °C was improved. This was achieved by reducing the rate of weight loss, maintaining the pH, textural stabilities, and color, and reducing the growth of microbes and lipid oxidation in the sausage samples. Based on these results, these edible films could be a fantastic alternative to traditional packaging materials for preserving Harbin red sausage [152]. Edible packaging made of guar gum and chitosan with orange essential oil nanoemulsion can keep cheese's quality and safety intact by preventing bacterial growth and lipid oxidation while stabilizing weight loss, pH, color, and textural changes [153]. Zhangyao, Hu [154] stated that applying 0.5% sodium alginate (SA) and 0.3% natamycin (NA) as an edible coating preserved the greenness and moisture content in the tomato calyx and pedicel by inhibiting browning, membrane leakage, and chlorophyll degradation; this technique can augment tomato fruit quality and elevate customer purchasing inclination.

10 Recent Advances in Biopolymer Composite Materials

Synthetic polymers, such as polyacrylate derivatives, are extensively utilized to produce high-performance adsorbent materials. Notably, due to environmental considerations, natural polymers like polysaccharides have garnered significant attention and can be effectively integrated with or without synthetic polymers to form hydrogels; importantly, polysaccharides facilitate the development of efficient hydrogels for wastewater treatment. Various fillers, including graphene derivatives, clays, and organic and inorganic materials are integrated into the hydrogel matrix to improve the hydrogels' chemical and thermal stability, mechanical strength, and adsorption efficiency [155]. Composite hydrogels based on polysaccharides seem to be the best option for removing methylene blue (MB) due to their enormous surface area, outstanding mechanical qualities, swelling capacity, and ability to be mass-produced. The biodegradability, non-toxicity, and high surface area of hydrogels derived from polysaccharides (alginate, CS, CE, SH, kappa-carrageenan [κ -CG], and Xanthan gum [XG]) have made them widely used in fields like agriculture, biomedicine, and wastewater purification. The presence of different functional groups on the surface of these hydrogels makes them excellent MB adsorbents. Additionally, by attaching inorganic substances or synthetic polymers to the hydrogel, mechanical strength is further increased, leading to composite hydrogels that are even more efficient at MB adsorption [155, 156].

11 Mechanisms of Control Release

A crucial component of biopolymer-based delivery systems is controlled release mechanisms, which dictate the pace, location, and timing at which bioactive substances become accessible [157]. Recent developments have concentrated on creating systems with precisely customized release profiles for particular applications, from quick release for sensory qualities to sustained release for extended usefulness. These processes usually depend on several triggers, including temperature fluctuations, enzyme breakdown, pH shifts, and mechanical stress [158]. The development of multiresponsive release systems, which combine several release mechanisms to accomplish complicated delivery profiles, has advanced significantly between 2018 and 2024 [159]. To optimize the transport of probiotics throughout the gastrointestinal tract, Wang et al. (2022) created a dual-responsive chitosan–alginate system that showed pH-dependent release in the stomach followed by enzymatic breakdown in the intestine. Similarly, cyclodextrin-protein complexes that respond to heat have demonstrated the ability to release flavors in a regulated manner during cooking [160]. Delivery systems with accurate release profiles can now be logically designed thanks to advancements in mathematical modeling and simulation approaches that have improved the predictability of release kinetics under various situations. In addition, state-of-the-art manufacturing processes like 3D printing and

microfluidics have made it possible to create intricate hierarchical structures that can control the release of substances in specific locations. This provides an enormous advance in the field of personalized nutrition applications since it enables the tailoring of release profiles to fit individual needs and preferences [161].

12 Smart Materials and Responsive Systems

12.1 *Stimuli-Responsive Materials*

The domain of stimulus-responsive materials and biopolymers has emerged as a transformative area in materials research, with unparalleled potential for developing dynamic systems that can adjust to their surroundings through programmed reactions to specific stimuli. These advanced materials demonstrate exceptional adaptability across several applications, including biomedical devices, controlled drug delivery systems, smart packaging, and environmental cleanup technologies. Their responsive behavior at the molecular level arises from meticulously designed structural components that experience conformational alterations, association/dissociation events, or chemical transformations in response to specific stimuli, facilitating exceptional functionality unattainable by conventional static materials.

Stimuli-responsive materials/biopolymers can alter their structure and other physicochemical characteristics in response to various external or internal stimuli, such as pH, temperature, light, mechanical forces, ionic strength, biomolecules, or magnetic and electric fields [162]. These changes influence the structural behavior of stimuli-responsive materials, which can be classified as chemical, physical, or biological as shown in Fig. 3. Physical stimuli include light, temperature, electric fields, humidity, and magnetic fields. Chemical stimuli include pH, redox conditions, and ionic strength. Biological stimuli, such as glucose or enzymes responsiveness, involve molecular functions such as enzyme reactions or receptor recognition of molecules. This understanding has become the foundation for creating materials applicable to various industries [163].

These stimuli-responsive materials can be divided into single- and multiresponse materials. Single-response materials are those that can alter their appearance and chemical or physical properties in response to a single environmental stimulus, such as light, pH, temperature, or electricity. These materials are valuable in applications like smart food packaging, active packaging, and the precise delivery of bioactive compounds [164]. The term “multistimuli” is increasingly used to describe the ability of biopolymers to react to multiple factors [165].

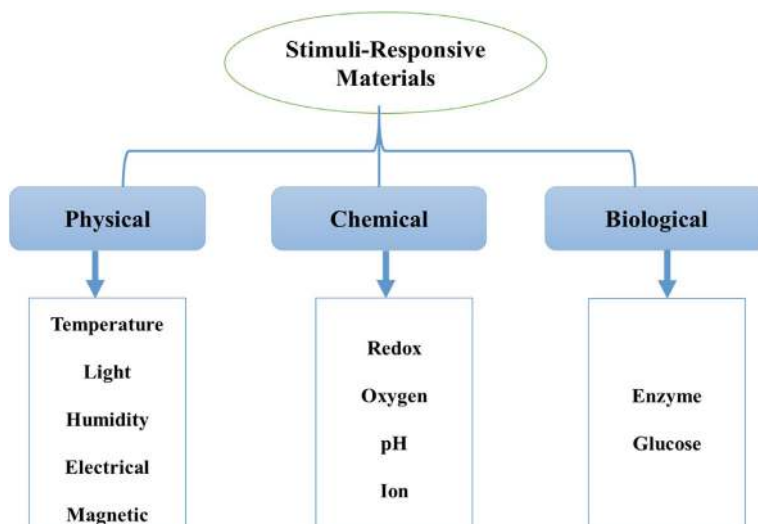


Fig. 3 Schematic diagram of stimuli-responsive material types

12.1.1 Humidity-Responsive Materials (HRM)

Materials responsive to humidity exhibit discoloration and deformation when subjected to changes in the surrounding environment's relative humidity [166]. Humidity-responsive discoloration materials are classified into self-discoloration and assisted discoloration types. Self-discoloration is driven by molecular changes and photodegradation, while assisted discoloration requires external elements to facilitate color change [166]. Regarding self-discoloration, films made from cellulose nanocrystals (CNCs) exhibit remarkable sensitivity to relative humidity (RH) changes, as mentioned by [167]. The color of these films shifts from green to red as RH ranges from 11 to 97%. By modifying the synthesis process, the CNC film's color shifts from green (at 50% RH) to orange-red (at 90% RH).

The deformation induced by HRM may happen due to hydrogen bonding, pH-responsive behavior, electrostatic interactions, and hydrophilic interactions between the material and water molecules [168]. Muñoz-Shugulí, Rodríguez-Mercado [169] used β -cyclodextrin (base material) and allyl isothiocyanate (an antibacterial agent) to create a humidity-responsive active packaging material. The material's response to humidity was linked to the β -cyclodextrin structure deformation. Moreover, multistimulus-responsive fibers were developed through electrospinning, incorporating cellulose nanocrystals (CNCs), zein (a protein), and starch [170]. These fibers were infused with natural antibacterial agents, such as thyme oil and citric acid, facilitating the production of antibacterial bioactive compounds when exposed to high RH. Therefore, the dual functionality of humidity-induced discoloration and deformation makes these materials particularly useful for applications like intelligent food packaging.

Recent improvements in humidity-responsive polymers have broadened their potential applications beyond traditional packaging methods. Researchers have created composite hydrogels that include sophisticated nanomaterials like graphene oxide and responsive polymers, resulting in materials with improved sensitivity and accelerated reaction times to humidity variations [171]. These composites have remarkable moisture-dependent mechanical capabilities, displaying substantial volume alterations and variations in mechanical strength that may be accurately adjusted to certain humidity levels. The integration of fluorescent indicators into humidity-responsive matrices has facilitated the creation of quantitative visual humidity sensors that exhibit gradient color responses directly corresponding to specific humidity percentages, thus delivering more accurate information than conventional binary indicators. This accuracy has rendered these materials more essential in pharmaceutical storage, electronics safeguarding, and cultural property conservation, where even slight humidity fluctuations can result in considerable harm [172].

12.1.2 pH-Responsive Materials

pH-responsive materials change color or deform due to variations in the pH of the environment. Spoilage of food releases acidic gases that change the surrounding pH. The change in pH induces alteration in the chemical structure of the responsive molecules within the pH-sensitive discoloration packaging, resulting in color changes at different pH levels [173]. Furthermore, deformation responses can include bending or “ON–OFF” switch-like deformations. These deformations are driven by functional groups on the biopolymer backbone, which ionize in response to pH fluctuations, causing a redistribution of charge density in the materials [174].

The redistribution of charges induces electrostatic repulsion or attraction among polymer chains, culminating in swelling or shrinking behaviors that present as macroscopic deformations. The extent of ionization is directly related to the ambient pH, enabling customizable and reversible responses that may be designed for certain pH thresholds [175]. Common pH-responsive functional groups encompass carboxylic acids, amines, and phenolic compounds, each possessing unique pKa values and hence reacting to varying pH ranges [176].

In food packaging applications, these materials can be included into intelligent packaging systems that offer real-time visual indications of food quality and safety. For example, anthocyanins derived from red cabbage or other botanical sources display notable color variations throughout a broad pH range, facilitating the progressive assessment of food freshness [177]. Likewise, synthetic pH indicators such as bromothymol blue or methyl red can be included into packing sheets to facilitate accurate color transitions at specified pH levels [178].

In addition to basic color alterations, intricate reactions may be developed by including other pH-sensitive elements. For instance, bilayer architectures consisting of hydrophilic pH-responsive layers paired with hydrophobic non-responsive layers can provide regulated bending behaviors due to differential swelling. This idea has

been utilized to create self-folding food packaging that autonomously seals upon exposure to microbial development, successfully confining possible contaminants [179, 180].

Research on pH-responsive materials has increasingly concentrated on natural and biodegradable polymers, such as bacterial cellulose nanofibers, chitosan, gellan gum/purple sweet potato, and starch-cellulose, for the immobilization of pH-sensitive dyes [181]. A study by Tirtashi, Moradi [181] found that an anthocyanin-based indicator was effectively developed using chitosan and cellulose to create a colorimetric pH indicator, which can monitor spoilage in milk without needing sophisticated instruments. Over a pH range of 2–11, the colorimetric pH indicator changed from pink to khaki, stayed stable for a month at 20 °C, and effectively identified milk spoiling by converting from blue to violet rose after 48 h of storage at 20 °C.

Purple sweet potato (PSP), is known for its antioxidant activity and health benefits. Active gellan gum/purple sweet potato composite films for pH detection have been developed by Wei, Cheng [182]. These intelligent films detected pH changes caused by *Escherichia coli* growth, with color changes from purple (initial) to blue (6 h) and yellow-green (24 h). The gellan gum/PSP film demonstrated potential as an active packaging material with enhanced antioxidant, mechanical properties, and water resistance, and it could serve as a simple indicator for detecting spoilage in protein-rich foods caused by bacterial growth.

Fish, one of the most widely consumed products worldwide, is highly susceptible to microbial spoilage, which increases its pH due to the accumulation of volatile nitrogen bases. In this context, Silva-Pereira, Teixeira [183] developed a hydrogel film by casting starch, chitosan, and red cabbage extract, which acts as a natural pH indicator. The hydrogel film remained transparent at both room and refrigeration temperatures (4–7 °C). After packaging fish in the hydrogel film and storing it for 16 h at room temperature and 72 h at refrigeration temperature, the film gradually changed color from blue to yellow. This color change indicated an increase in pH, signaling fish spoilage due to microbial activity.

12.1.3 Temperature-Responsive Materials

Temperature is a crucial environmental factor that influences food quality, as fluctuations during the food's shelf life can decrease both its quality and safety. Therefore, adjusting temperature, and minimizing inter-color interference is essential for the performance of smart packaging applications.

The perception of sweetness, which significantly influences the acceptability of fruit, is also sensitive to temperature changes. To address this, color-switching indicators visible to the naked eye were created using encapsulated thermochromic materials to indicate the ideal temperature for consuming watermelons [184]. The results showed that the color-switching behaviors were purple, red, and gray at (below 6 °C), (9–11 °C), and (above 13 °C), respectively. At 9.1 ± 0.4 °C, the watermelon became red and faded dramatically at 12.2 ± 0.5 °C, suggesting optimal temperature and the best taste. Temperature-responsive hydrogels undergo volume changes

in response to temperature variations. Positively responsive systems, which have an upper critical solution temperature (UCST), and negatively responsive systems, which have a lower critical solution temperature (LCST), are the two major categories of these hydrogels [185]. In the food industry, various biopolymers can be used to create temperature-responsive hydrogels. For example, gelatin molecules contain helical structures at lower temperatures, facilitating the hydrogel formation through hydrogen bonding between helical regions of different molecules [185]. Above the LCST, the copolymer chains collapse, promoting the production of quercetin contained within the mesopores. The hydrogel produced significantly more quercetin at 40 °C (>LCST) compared with 20 °C (<LCST), with a difference of 11.8%–20% [168].

N-isopropyl acrylamide and N-tert-butyl acrylamide biomaterials are commonly utilized for the creation of temperature-responsive materials in the food industry [185]. These hydrogels feature a low-temperature response between 8 and 10 °C and offer high sensitivity for monitoring temperature with an accuracy of approximately 2 °C. It also exhibits a 90% volume expansion, demonstrating great potential for various applications, especially in monitoring food product temperature.

Temperature-responsive materials in smart packaging serve as real-time monitoring systems that provide ongoing evaluation of product exposure to essential temperature conditions within the supply chain. These materials often include specialized polymers or composites that demonstrate consistent physical or chemical alterations upon surpassing designated temperature limits. Irreversible thermochromic indicators offer permanent proof of temperature abuse throughout transport or storage, while reversible systems enable customers to evaluate the actual product temperature prior to use. The incorporation of these responsive features with developing technologies like printed electronics and wireless communication systems has augmented their functionality by facilitating automated data collecting and remote monitoring capabilities. The globalization and complexity of food supply chains need the advancement of sophisticated temperature-responsive packaging materials that exhibit improved sensitivity, selectivity, and stability, presenting a substantial opportunity for the enhancement of food safety management systems.

Light-Responsive Materials

Light-responsive materials offer significant advantages across various applications, providing rapid and accurate responses under controlled conditions. Upon exposure to light, these materials undergo a phase change that makes them responsive to light. Using light as a stimulus offers various advantages, such as instant and precise application, along with adjustable wavelengths for controlling long-distance applications through fiber optic cables [186].

For instance, Yang, Tian [187] developed photochromic transparent wood (PTW) composite with a high transmittance of 85.5%, which responds to light stimuli. It turns colorless under sunlight and glows red under 365 nm UV light, exhibiting reversible optical changes. PTW can be used for invisible anti-counterfeiting applications, enabling secure information storage under visible light and decoding under UV light, even in black packaging.

In a different study, low-cost, low-loss, and adjustable food packaging film with sustained antibacterial activity, self-activation capabilities, and significant industrial potential has been explored by Ni et al. [186]. In this research, a chitosan/negatively charged graphitic carbon nitride self-activated bio-nanocomposite film was prepared. The film demonstrated antibacterial efficacy of $99.9 \pm 0.04\%$ against *S. aureus* and $99.8 \pm 0.26\%$ against *E. coli* when activated by visible light. Additionally, the film extended the storage period of tangerines to 24 days.

Furthermore, light-responsive hydrogels are increasingly used in food packaging to activate antibacterial properties, prevent microbial contamination, reduce food-borne disease risks, and extend shelf life [188]. Researchers have investigated the use of food-grade biopolymers for these hydrogels, presenting a promising area for future study. For example, Giammanco, Sosnofsky [189] developed visible light-responsive gels utilizing alginate and pectic acid, coordinated with Fe (III) ions. A hydrogel scaffold made with sodium alginate and oligomeric proanthocyanidins has been created to respond to near-infrared lasers [190]. Additionally, the photo response and controlled release of these light-responsive hydrogel materials can be modified by changing the metal coordination environment and the types of polysaccharides [185].

These materials have transformed disciplines from biomedical engineering to intelligent architecture, as they can be engineered to react to specific wavelengths across the electromagnetic spectrum—from ultraviolet to infrared—facilitating selective activation and advanced control mechanisms without physical contact or supplementary chemical agents. Moreover, their reaction may be optimized by molecular engineering to attain either reversible or irreversible conversions with differing speeds, rendering them very adaptable for various technological applications.

12.1.4 Electrical-Responsive Materials

The researchers developed a novel assay that converts electrochemical signals into optical readouts, which facilitates the visual detection of *Escherichia coli*. Electrochemical polymerization of polyaniline on indium tin oxide screen-printed electrodes was used to enable the visual detection of *Escherichia coli* [191]. The color of the polyaniline changes in response to varying *E. coli* concentrations, converting from blue-violet (penigraniline) to blue (emeraldine base), green (emeraldine salt), and yellow (leucoemeraldine salt), with lighter colors suggesting greater concentrations.

Electro-responsive materials research is still in its early stages, with more work needed to produce biocompatible and biophilic packaging options for accurately identifying changes in food quality. While these materials have the potential for regulated delivery and quality monitoring, their potential efficacy will depend on enhanced biocompatibility and response accuracy to enable long-term usage [168].

12.1.5 Enzyme-Responsive Materials

Enzyme-responsive materials react to the presence of specific enzymes. By utilizing enzyme characteristics, such as their capacity to catalyze physicochemical alterations and enable biorecognition, these polymers are highly valuable in creating systems, especially in environments where a particular enzyme is overexpressed. Enzyme-responsive polymers offer several benefits, including targeted action within cells, the ability to control secretion, a wide range of enzymes applicable across various uses, enhanced permeability, and improved degradation resistance [192]. However, the primary drawbacks include the risk of premature charge release if an enzyme has a similar structure, as well as the potential for the charge to be released before reaching its intended target [192, 193].

For instance, the microorganisms that spoil food contained within this material evolved by synthesizing pectinases to break down pectin into basic units and release thymol that inhibits further microbial growth. It has been shown that this material prevents the growth of numerous fungi and bacteria such as *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis*, and *Aspergillus niger*, all the while increasing the storage period of citrus fruits [194].

12.2 Biosensor in Food Industry

It's essential to monitor the safety and nutritional value of food, as it can contain harmful contaminants of organic, inorganic, and biological origins. To achieve this, biosensors play a critical role as biosensors are analytical instruments designed to convert input signals into a continuous output signal. It consists of two key components: a receptor and a transducer. The receptor is responsible for converting chemical or physical information into an energy form which is then transformed by the transducer into a meaningful analytical signal, typically in the form of an electrical output [195]. Several biosensors have been developed and evaluated for food purposes, including fluorescent sensors, microfluidic sensors, gas sensors, electrochemical/imprinted biosensors, immunosensors, and thermal sensors [195, 196].

12.2.1 Electrochemical Biosensors

Electrochemical biosensors are simple devices that convert biological information, derived from redox processes, into electrical signals. These sensors play a crucial role in identifying biomarkers and monitoring environmental pollutants by detecting various bioanalytes and chemicals [197]. Their myriad advantages, including user-friendliness, simplicity, high sensitivity, portability, rapid reaction times, cost-effectiveness, and environmental compatibility, have substantially facilitated their broad acceptance [198]. Electrochemical biosensors are categorized

into two primary types depending on their biological recognition mechanisms: (1) biocatalytic sensor devices and (2) optional biosensors [199].

Catalytic biosensors, which utilize various types of enzymes, account for half of the biosensor production [199], while, optional biosensors, where antibodies, membrane receptors, or nucleic acids are immobilized on the electrode [200]. Electrochemical biosensors can use the electrode as an amperometer, potentiometer, conductivity, and impedimetric converter to convert a chemical signal into a measurable electrical signal [200]. *Escherichia coli* is a pathogenic microorganism whose presence in vegetables serves as an indicator of food contamination [201]. A potentiometric electrochemical biosensor can be employed to identify *E. coli* in vegetables by monitoring the pH changes caused by its presence [201]. Furthermore, electrochemical biosensors are highly efficient in detecting small levels of trace metals like arsenic, lead, and cadmium. They have also been effectively used to detect paraoxon, carbaryl, aldicarb, and other pesticides in food items [201, 202].

12.2.2 Fluorescent Biosensors

Fluorescent biosensors are materials, such as reagents, proteins, or cells, that produce an analytical signal through photoluminescent emission (fluorescence or phosphorescence) or convert biological analytes into light signals [203]. These signals can be detected using various methods, including single fluorophores, Förster resonance energy transfer pairs, or pairs of identical fluorophores [204]. Fluorescent biosensors are used to monitor intracellular biochemical processes, such as metabolite changes or enzyme activity, as well as to detect environmentally harmful gases like nitric oxide and hydrogen sulfide [203, 205].

Examples of fluorescence-based biosensors include enzyme fluorescence and DNA fluorescence. Regarding enzyme fluorescence, a rapid fluorescent biosensor to detect pathogens was developed using a three-dimensional (3D) DNA walker and catalyzed hairpin assembly (CHA) reaction [206]. Their findings showed that detection limits as low as 22.9 CFU mL^{-1} for *Salmonella typhimurium* and 28.1 CFU mL^{-1} for *Escherichia coli* could be reached in 50 min due to the DNA walker's robust manipulation ability and CHA's significant signal amplification potential. Additionally, the biosensor exhibited excellent selectivity and high repeatability, with recovery rates ranging from 91 to 115% in real sample detection. Given these strengths, this template holds significant promise and great potential as a reliable tool for pathogen detection, with wide-ranging applications in global public health and food safety. This template has significant potential for routine pathogen detection in public health and food safety. In the context of DNA fluorescence, a simple fluorescent biosensor was developed to detect acrylamide (AM), a possible carcinogen formed during food thermal processing, using single-stranded DNA (ssDNA) and carbon quantum dots (CQDs) [207]. Their results showed that the attachment of ssDNA caused a reduction in the fluorescence intensity of CQDs at 445 nm (excited at 350 nm). The biosensor demonstrated a low detection limit of $2.41 \times 10^{-8} \text{ M}$ and a linear detection range from 5×10^{-3} to $1 \times 10^{-7} \text{ M}$. Furthermore, the biosensor showed good recovery

(91.36–98.11%) in bread crust, indicating its potential for practical applications in detecting AM in food.

12.2.3 Gas Sensors

Gas sensors have crucial roles in leakage monitoring of gas within food packaging by evaluating spoilage gases like nitrogen and oxygen as well as carbon dioxide. They offer a quick, sensitive method to detect carbamate pesticides in vegetables, fruits, and meat products rancidity [195]. The structure of the gas sensor consists of three parts, two electrodes and a sensing electrode which is the working electrode, counter electrode and reference electrode. A divided thin layer forms the counter electrode. While the working electrode is at a fixed potential, contact is made to the reference electrode. A hydrophobic layer allows gas to permeate, contact the working electrode, which generates electrochemical signal by the sensing element to the target gas [195].

Carbon dioxide is one of the gas sensors which is uniquely designed for measuring CO₂ levels in food packaging. These gas sensors have numerous benefits when compared with other methods like the extensive range of use in dangerous environments, attitude to target gas molecules, and resistance to electromagnetic interference [208]. Food spoilage processes have gases that mark and include ammonia (NH₃) and hydrogen sulfide (H₂S) as the main gases. In protein-rich foods such as eggs, dairy products, and meat, NH₃ and H₂S serve as indications of freshness; these gases may also be released by decomposing crops, such as spinach and maize [187]. Yuan et al. [209] conducted research demonstrating the use of n-doped bulk silicon-based chemical-sensitive field-effect transistors (CSFETs) for the multiplexed detection of trace gases, such as NH₃, H₂S, and H₂O, to assess food safety and quality. CSFETs covered with sensing materials comprising ruthenium, silver, and silicon oxide are utilized to attain stable responses at ambient temperature for hydrogen sulfide (H₂S), ammonia (NH₃), and humidity. Their findings shown that a multi-CSFET sensor shows a signal variation of 13.34 from its baseline when subjected to 1 ppm of NH₃, 724.45 under 1 ppm of H₂S, and 23.46 under 80% relative humidity, with detection sensitivity reaching as low as 10 ppb for both NH₃ and H₂S.

Polymer-based gas sensors function through different processes that boost their usability in food packaging applications. These sensors typically work through the detection of changes in electrical conductivity or resistance when target gases contact with the detecting polymer matrix. Conducting polymers including polyaniline (PANI), polypyrrole (PPy), and polythiophene (PTh) experience reversible doping and dedoping when exposed to certain gases, leading to quantifiable changes in their electrical properties. The method entails gas molecules adsorbing onto the polymer surface or permeating the polymer matrix, where they engage with the polymer chains via many interactions, including electron transfer, hydrogen bonding, or dipole–dipole interactions. This contact disturbs the electronic configuration of the polymer, altering its charge carrier density and mobility, which in turn affects the electrical conductivity. The selectivity of polymer gas sensors can be improved by

integrating functional groups or nanoparticles that specifically interact with target gases. Moreover, polymer nanocomposites that integrate conductive polymers with metal oxides or carbon nanomaterials exhibit enhanced sensitivity and stability for the detection of food spoilage gases at parts-per-billion concentrations, providing substantial benefits for real-time monitoring in intelligent packaging systems [210].

13 Migration and Safety Risk Assessment

The increasing demand for biopolymers in food packaging is propelled by the necessity for sustainable alternatives to traditional packaging materials. Biopolymers provide renewability, biodegradability, and biocompatibility, possibly mitigating the environmental issues associated with conventional plastics [211]. When appropriately manufactured, these materials are acceptable for ingestion by both animals and humans, posing no health hazards. Nonetheless, guaranteeing the safety of food packaging materials is essential, especially for food interactions [212].

Assessing the potential migration of biopolymer-based packaging into food is the preliminary phase in identifying probable risks for a thorough consumer safety risk evaluation [213]. Migration testing often uses food simulants that replicate the chemical compositions of diverse food products, or the real food items themselves. These studies are crucial for assessing possible chemical leaching from packaging materials under-regulated settings [213]. Migration rates are affected by several parameters, including the physicochemical properties of migrants, the kind of packing material, the food product, temperature, storage duration, and the ratio of packaging surface area to food weight [214].

All food-contact materials must adhere to Commission Regulation No. 1935/2004/EC [215] to guarantee food safety. Furthermore, plastic materials must comply with Commission Regulation No. 10/2011, which sets down strict migration limits for chemicals authorized in food-contact plastics [216]. Moreover, inadvertently introduced chemicals absent from any affirmative listings in the rule must not surpass $0.01 \mu\text{g g}^{-1}$ in food or simulant, therefore confirming they are non-carcinogenic, non-mutagenic, and non-reprotoxic. This movement may encompass both non-volatile and volatile chemicals, possibly modifying the organoleptic qualities of food [217]. Therefore, the chemicals migration from food packaging materials necessitates stringent monitoring to maintain adherence to food safety rules and to avert negative impacts on consumer health [217].

Numerous research studies have examined compounds' migration from diverse biopolymer-based food packaging materials, emphasizing safety concerns. A research investigated the migration of silver nanoparticles (AgNP) from starch-based edible coatings on sausages [218]. The initial concentration of AgNP in the coating solution was $23.47 \mu\text{g/mL}$. Subsequent to the application to sausages, the retained AgNP concentration diminished to 5.3 ng/g , with a further decline to 4 ng/g after washing and cooking. This work underscores the need of evaluating nanoparticle migration in food packaging, since these particles may influence food sensory

attributes. Furthermore, the migration of nanoparticles from smart packaging materials, including those with titanium dioxide (TiO_2), may result in food spoiling, especially in lipid-based goods, due to lipid oxidation [218].

The use of sophisticated mass spectrometry techniques, such as Direct Analysis in Real Time (DART) and ambient ionization methods, is essential for the rapid and efficient identification of migration chemicals from food packaging materials [217]. DART mass spectrometry provides swift analysis (under 60 s per sample) and the capability to examine both solid and liquid materials with little preparatory requirements. These approaches are essential for the routine assessment of food packaging safety, allowing the rapid identification of both volatile and non-volatile chemicals moving from packaging materials into food. The capacity to conduct such analyses without intricate sample preparation renders these approaches especially beneficial for guaranteeing adherence to safety standards and regulations in food packaging [217].

A significant study examined the migration of compounds from bamboo-derived biopolymers utilized in food packaging. This study performed migration experiments with several solvents, namely 10% ethanol, 3% acetic acid, and 95% ethanol [217]. Gas chromatography-mass spectrometry (GC-MS) analysis found 25 volatile and semi-volatile chemicals, including phytosterols, in the 95% ethanol solution. Furthermore, non-volatile chemicals, including melamine and its derivatives, were identified and quantified utilizing ultra-performance liquid chromatography in conjunction with time-of-flight mass spectrometry (UPLC-Q/ToF). Melamine migration surpassed 50 mg/Kg in a migration test, prompting worries about potential health hazards. The research utilized DART mass spectrometry, facilitating the rapid and concurrent identification of both volatile and non-volatile migrants. This method demonstrated efficacy in rapidly evaluating chemical migration from biopolymer packaging, presenting a viable strategy for assuring adherence to food safety laws [217].

The migration of oligomers from a poly(lactic acid) (PLA)-polyester blend used in food packaging was also investigated [215]. The study utilized food simulants, such as 3% acetic acid and juice, to test migration levels. A total of 21 oligomers were identified, with 9 originating from PLA and 12 from the polyester component of the blend. The study utilized fabric phase sorptive extraction (FPSE) for the extraction and pre-concentration of the oligomers. This technique successfully identified three new compounds not detected by direct injection, demonstrating its value in uncovering migration compounds that would otherwise go undetected. Two PLA oligomers, cyclic $(\text{LA})_6$ and linear $\text{HO}-(\text{LA})_4-\text{H}$, were isolated with high purity, and the concentration of oligomer $[\text{AA-BD}]_2$ was found to be 22.63 $\mu\text{g/g}$ in acetic acid and 19.64 $\mu\text{g/g}$ in juice, while the concentration of other oligomers was below the regulatory threshold of 7.56 $\mu\text{g/g}$.

Additionally, another study developed poly (lactic acid) (PLA)-based biocomposite films incorporating algal cellulose nanocrystals (CNC) and curcumin (CUR) as a bioactive agent. Creating two types of biocomposites, with and without CUR, and varying CNC concentrations [219]. Migration studies showed that CNC increased the overall migration (OM) rate of the films, though it remained within safe limits [219].

Besides migration tests, conducting toxicological risk assessments and evaluating dietary exposure are essential for ensuring the safety of edible packaging materials [213]. Zhao et al., [213] evaluated the safety of hydroxypropylated-phosphated-modified glutinous rice starch through acute and 28-day repeated oral toxicity tests. The results indicated that the modified starch had a value of more than 120,000 mg/kg LD50, classifying it as non-toxic. Additionally, the recommended daily intake for a 70 kg person was found to be below 38,900 mg, indicating that the recommended intake should not exceed 38,900 mg/day, suggesting a safe consumption level. Al-Asmar et al. [220] coated potato sticks with chitosan or pectin hydrocolloids prior to frying to minimize the levels of acrylamide and oil in French fries.

The impact of sulfuric acid hydrolysis duration (30, 60, or 90 min) on the cytotoxicity of needle-like CNCs derived from wheat bran cellulose was examined using Caco-2 cells. The cells were subjected to CNC concentrations range of 50–5000 µg/mL for 24 h [221]. Their results found that Cell viability did not show a significant impact following exposure to three different concentrations of cellulose nanocrystals (CNCs) up to 2000 µg/mL; however, a decrease in viability (<80%) was shown at a concentration of 5000 µg/mL of CNCs. Furthermore, no cytotoxic effects were detected after a 72-h exposure to CNC concentrations ranging from 0 to 5 µg/mL, derived from cotton linters, when tested on both undifferentiated and differentiated Caco-2/TC7 cells [222]. In a different study, no signs of CNC uptake by differentiated Caco-2 cells were observed, nor did it observe any cytotoxicity at concentrations up to 10 mg/mL [223].

14 Environmental Impact and Sustainability

The development and adoption of biopolymer-based composites in the food industry is primarily driven by their environmental impact. These materials present viable alternatives for traditional petroleum-based packaging as worries about plastic pollution and resource depletion grow. Recent studies have evaluated the sustainability profile of biopolymer composites, encompassing the extraction of raw materials and the management of end-of-life processes [224].

Significant progress has been achieved in creating biopolymer composites with improved environmental advantages while preserving essential functional features between 2020 and 2024. Food processing waste and agricultural byproducts have become particularly appealing sources for the extraction of biopolymers, supporting the ideas of the circular economy. For example, Pinaeva and Noskov (2024) showed how cellulose nanofibers derived from sugarcane bagasse may strengthen starch-based films for packaging applications, therefore resolving waste management issues and producing products with additional value [225].

The environmental trade-offs connected to different biopolymer composite processing techniques have also been the subject of recent studies. Certain cutting-edge methods can enhance material qualities, but they can also result in higher energy usage and a greater environmental impact [226]. Research on green processing

technologies, including solvent-free fabrication techniques, enzyme-assisted extraction, and microwave-assisted processing, which reduce environmental effects without sacrificing material performance, has increased as a result of this [227]. Life cycle assessments, biodegradability studies, recycling potential evaluations, and carbon footprint assessments are essential for determining the environmental impact and sustainability of biopolymer-based composites.

14.1 Life Cycle Assessment

For assessing the overall environmental effect of biopolymer-based composites in food applications, LCA has emerged as a crucial method. The core of LCA involves the creation of a model that quantifies the inputs and outputs associated with each phase of the product's life cycle. The boundaries of the assessment can vary based on its objective; for instance, a "cradle-to-gate" assessment may be appropriate for comparing two alternative processes for the same product, whereas a "gate-to-grave" assessment could be sufficient for evaluating different end-of-life technologies [228].

In order to provide a more comprehensive picture of sustainability performance, recent LCA studies have extended beyond standard impact categories to include implications on biodiversity, land usage, and water footprint. To assist industry stakeholders in making decisions, these evaluations usually compare biopolymer composites with traditional materials across a variety of environmental indices [229, 230].

The standardization of LCA techniques, particularly for biopolymer composites, has been a noteworthy advancement between 2020 and 2024, resolving earlier discrepancies in system boundaries and allocation techniques [230]. This standardization has increased the trustworthiness of sustainability claims and improved comparability between research. For instance, contrasted chitosan–gelatin composite films with traditional polyethylene packaging for fresh produce and showed 40–60% reductions in the potential for global warming and the depletion of fossil resources, albeit with possible trade-offs in water and land use [231].

For instance, Salwa et al. [232] conducted a LCA of a natural fiber-reinforced biopolymer composite takeout food container, evaluating its environmental impacts from a cradle-to-grave perspective. The study revealed that the total human health damage from the containers was 2.63×10^{-5} daily and ecosystem damage of 9.46×10^{-8} species. year per kilogram of containers. Additionally, the primary substances contributing to the "Particulate Matter Formation" impact category, which are responsible for respiratory diseases, include air/sulfur dioxide, air particulates ($<2.5 \mu\text{m}$), and air/nitrogen oxides, with corresponding metrics of 1.9×10^{-6} daily per kilogram of containers, 2.75×10^{-6} daily and 2.93×10^{-6} daily, respectively.

The significance of regional characteristics in influencing environmental performance has also been emphasized by recent LCA studies. Depending on regional agricultural methods, energy supplies, waste management facilities, and travel distances,

the sustainability advantages of biopolymer composites might differ greatly. Regionalized LCA models that take these variances into consideration have been developed as a result of this discovery, offering more precise evaluations for certain implementation scenarios [233, 234]

14.2 Biodegradability Studies

One significant benefit of biopolymer composites over traditional packaging materials is their biodegradability, which may lessen trash buildup in natural settings. To give thorough assessments of degrading behavior, recent biodegradability studies have used standardized testing procedures in a variety of settings, such as soil burial, home and industrial composting, and aquatic habitats. These investigations evaluate the possible production of microplastics or hazardous byproducts, in addition to the pace and degree of biodegradation [235–237].

Biodegradability in Soil

Over time, various geological, biological, and hydrological processes have shaped the Earth's crust, creating porous land surfaces typically referred to as soil [238]. The complexity and variability of natural factors result in soils with diverse conditions, including unique temperatures, pH levels, moisture content, and oxygen concentrations, which in turn influence the activity and composition of local microbiota [239]. As a result, soils are among the most biodiverse ecosystems, with a single gram of soil containing approximately 10 billion microorganisms, including thousands of unique bacterial and fungal species [239]. Biodegradation, the breakdown of macromolecular compounds by microorganisms, is particularly relevant in soils due to the abundance of microbial life. This makes soils a more suitable environment for studying the degradability of biopolymers compared to other ecosystems [240].

Several studies reveal that a variety of techniques are being used to assess the biodegradation of biopolymers in soil, as there are currently no established European or international standards or criteria for this process [238]. For instance, under natural conditions, the complete degradation of poly(lactic acid) may require several years [241], with degradation initiation also taking considerable time, as shown by an eleven-month study conducted in Mediterranean soil [238]. In contrast, a bio-based film consisting of starch and poly(vinyl alcohol) reached 90% biodegradation in 28 days utilizing a similar soil burial approach technique [242]. These examples highlight that each biopolymer degrades differently, influenced by intrinsic factors such as crystallinity, surface area, molecular weight, chemical structure, and cross-linking, as well as environmental factors like microbial composition, temperature, microbial composition humidity, and pH [243].

An experimental study on starch-based polymers demonstrated increased degradation with higher starch concentrations, resulting in enhanced degradation efficiency, reaching approximately 95% [190]. The rate of biodegradation was increased in moist conditions due to hydrolysis and microbial activity. When buried in

soil, a starch-based polymer film decomposed more quickly and lost its weight within 7 days, but PLA, poly(butylene succinate-co-butylene adipate) (PBSA), and polyhydroxyalkanoates (PHAs) retained their weight for roughly 84 days [244].

Films made from a blend of Chitosan /thyme essential oil combined with zinc oxide (ZnO), polyethylene glycol, nano clay, and calcium chloride exhibit low water vapor transmission rates, high tensile strength, and are both water-soluble and biodegradable. Additionally, Chitosan /thyme essential oil films exhibit the highest rate of biodegradation over 28 days [245]. Likewise, chitosan/mustard oil films underwent 45–70% degradation after being buried in soil for 21 days [246].

Biodegradability in Compost

Composting is an aerobic process where microorganisms decompose biodegradable materials into humus under controlled conditions, which enriches the soil and improves agricultural productivity. It also helps mitigate waste disposal challenges and reduce greenhouse gas emissions, as compost can be reused as a valuable organic resource [247]. Both international and national regulations promote using of composting for managing organic waste, including waste containing biopolymers. A key regulation in waste management, the “European Directive 1999/31/EC on the Landfill of Waste” [248], emphasizes the importance of recycling and lowering the volume of biodegradable waste disposed of in landfills. This is particularly relevant in developing countries, where the quantity of biodegradable waste is substantial. As a result, composting has become an essential component of effective waste management strategies [247].

Understanding the biodegradation processes of complex biopolymer composites with many components has advanced significantly between 2020 and 2024 [236]. In their investigation of the biodegradation patterns of starch–PLA–nanoclay composites, for example, Freitas et al. [249] found that although the starch component disintegrated quickly, the addition of nano clays somewhat postponed PLA breakdown under composting conditions. The creation of composites with programmable deterioration profiles appropriate for various applications and end-of-life situations has been guided by this concept [250].

Several studies have evaluated the degradation of film packaging under composting conditions. Alginate composite films derived from *Sargassum natans* seaweed showed degradation after 14 days under simulated conditions [229]. Deformation and an increase in opacity were shown in the first week, signaling the initiation of hydrolytic degradation, leading to crystallization and cracking of the alginate composite film matrix. In a similar, polybutylene adipate terephthalate (PBAT) films modified with hydroxypropylated starch and native starch achieved 99% biodegradation by day 8, while PBAT/acetylated starch and PBAT/octenyl-succinated starch reached biodegradation level of 97% and 98% by days 9 and 11, respectively [251].

Furthermore, the properties of the composite film or mixture have a great impact on the rate of film degradation during composting. Incorporating biodegradable components such as chitosan, starch, and protein, for example, might increase the film’s hydrophilicity and speed up its degradation. Furthermore, environmental parameters

like humidity and temperature in the composting environment influence the rate of disintegration [252].

Biodegradability in Aquatic Systems

The aquatic ecosystem encompasses diverse habitats with varying environmental conditions, each influencing biopolymer biodegradability in unique ways, making it more challenging to predict than in terrestrial environments [253]. For example, the water surface, with its moderate temperatures, UV light, and oxygen, accelerates abiotic degradation, while deep waters lack these factors, slowing degradation. Additionally, freshwater, which has a higher microorganism concentration, promotes faster hydrolysis compared to seawater, which is salt-rich. The material's density also affects the degradation rate, with plastics floating on the surface degrading differently than those in deeper waters [254].

Abdillah and Charles [255] conducted a thorough study of arrowroot starch / carrageenan-based films biodegradation rates in both composite and seawater environments. They found that the blend films of arrowroot starch 4% + carrageenan 0% and arrowroot starch 3.5% + carrageenan 0.5% were completely degraded after 7 days in a compost environment and 42 days in seawater. This notable difference is due to the slower degradation of plastic materials in seawater, where there is reduced exposure to thermal oxidation. Moreover, films degrade more quickly in soil than in water, as the water environment tends to have lower temperatures and a less abundant microbial population. The biodegradability of films in aquatic environments is also significantly impacted by factors such as climate, light, and other environmental conditions [256].

The biodegradation rate (%) of various biopolymer films in an aquatic system was assessed by measuring dissolved oxygen (DO) levels (mg O₂/l) over 28 days [257]. The results showed gelatin and sodium caseinate natural biopolymer films achieved full degradation (100%) by day 1. In contrast, poly(vinyl alcohol) (PVA) and poly(lactic acid) (PLA) synthetic biopolymer films achieved a maximum biodegradation of $56.3 \pm 0.7\%$ (PVA) and $38.0 \pm 4.3\%$ (PLA) by day 14 (Fig. 4).

The difficulty of striking a balance between biodegradability and functional needs like mechanical strength and water resistance has also been the subject of recent studies. Materials that retain stability while in use yet efficiently biodegrade after disposal have been produced using a variety of techniques, such as selective cross-linking and multilayer architectures. Furthermore, under some circumstances, adding additives that promote biodegradation—such as certain enzymes and microbes—has shown promise in hastening the breakdown of more resilient biopolymers [237, 246].

14.3 Recycling Potential

Recycling is another crucial route for reducing environmental effects, even though biodegradability provides a significant end-of-life alternative for biopolymer composites. The recyclability of several biopolymer composite materials has been

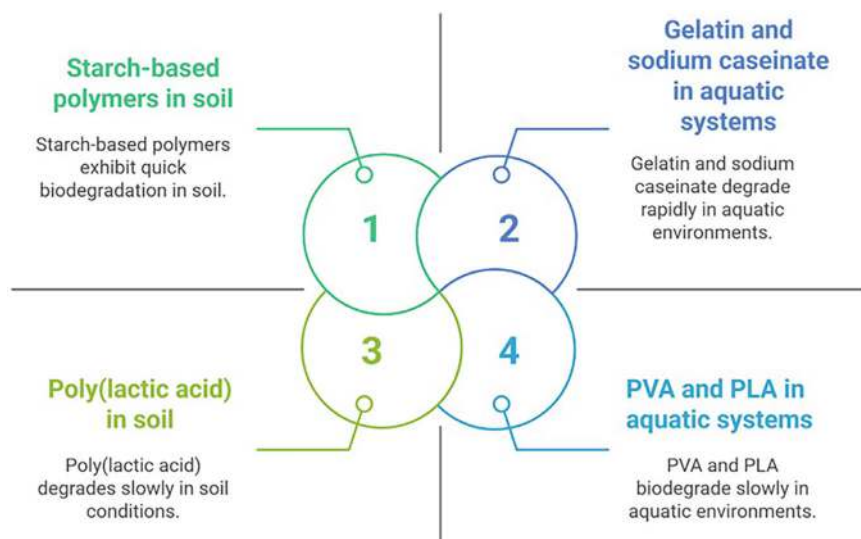


Fig. 4 Comparative biodegradability of common biopolymers

assessed recently, with an emphasis on practical implementation issues as well as technological viability. These investigations determine possible contamination problems in current recycling streams and evaluate how material qualities vary over several processing cycles [258, 259]. The creation of biopolymer composites that are specially optimized for recyclability has been a noteworthy advancement in the last period. These materials have selective solubility, thermally reversible bonding, or reversible cross-linking processes that make it easier to separate and recover component materials [260, 261]. In order to facilitate efficient component recovery and reprocessing, He et al. [262] created a chitosan–cellulose composite film with pH-responsive adhesive layers that were easily detached under slightly alkaline circumstances. The suitability of biopolymer composites with the current recycling infrastructure has also been investigated recently, with possible integration paths and required modifications identified. Certain biopolymer composites have the potential to be used in coprocessing or specific recycling channels, while others may interfere with traditional plastic recycling streams. Furthermore, new recycling methods have shown promise for reclaiming value from increasingly complex biopolymer composite architectures, such as chemical and biological recycling techniques [263, 264].

14.4 Carbon Footprint Analysis

As the food sector looks to cut greenhouse gas emissions across its value chain, carbon footprint analysis has grown in significance for assessing the climate effect of biopolymer-based composites [265]. The carbon footprint of several biopolymer materials has been measured recently, considering emissions related to the manufacturing of raw materials, processing, transportation, usage phase, and end-of-life management. These studies offer vital information for process optimization and material selection that takes climate change into account [266].

Like any product, bio-based plastics, with their bio-polyethylene, bio-polypropylene, bio-poly(ethylene terephthalate), etc., contain primary and secondary energy as well as materials. Carbon footprint definition used to summarize all these elements into a single value. In the case of plastics, global warming potential becomes an important issue since a relatively high amount of materials are needed to store and transport beneficial products, and the relevant use or end-of-life phase may involve long times in which the remaining low molecular weight molecules are still able to absorb solar radiation and contribute to Earth temperature increase, triggering climate change. Studies prove that bio-based polymers, compostable or not, are not always “greener” than conventional ones and may even have a global warming potential almost as high as high-density polyethylene. So, remarkable care is needed when designing bio-packaging to reduce the probability of any potential environmental stress. Ethylene is the building block of polyethylene, the widest produced and utilized plastic in the world but, in the meantime, it is the main monomer of the bio-polyethylene patented process, considering that it may be obtained from ethanol, which is derived from sugarcane. Sugar is annual renewable cultivation with a three-month period between harvests, which makes bio-polyethylene an intra- and inter-annually stable and controllable polymer. For these reasons, bio-polyethylene is considered a renewable polymer. In 2018, worldwide 2% of plastics were produced in bio-based plastics, and 20% in bio-packaging, meaning 10 million tons, outlets are forecasted to rise to 15% in 2022 and to get 15% of its final use in packaging in 2030. Bio-poly(ethylene terephthalate) became available in the form of textile fiber, which is ideal for circular clothing strategies at the end of the garment life.

Given the potential climatic advantages of carbon storage in bio-based materials, biogenic carbon accounting has been incorporated into carbon footprint assessments [233]. These updated approaches provide more realistic depictions of climate impacts by differentiating between carbon fluxes that originate from fossil fuels and those that are biogenic. For example, when taking into consideration carbon sequestration during biomass growth and suitable end-of-life scenarios, alginate-based composites made from sustainably harvested seaweed might reach carbon neutrality [267, 268]. The significance of land-use change and farming methods in affecting the total carbon footprint of biopolymer feedstocks has also been emphasized by recent studies [269, 270]. The carbon intensity of biopolymer production may be considerably decreased by using sustainable agricultural practices, such as agroforestry, precision agriculture, and organic farming. Furthermore, obtaining biopolymers from agricultural

leftovers and side streams instead of specific crops might reduce emissions associated with land-use change and increase resource efficiency [269]. These observations have influenced the creation of certification programs and sourcing criteria that assist producers in locating feedstock choices that are climate-optimal for the manufacturing of biopolymer composites [271, 272].

15 Current Challenges in Food Industry Applications

Although there have been encouraging developments, there are still many obstacles to the broad commercial use of biopolymer-based composites. The intrinsic heterogeneity of natural polymer characteristics is a major drawback that may impact industrial repeatability and standardization. Furthermore, compared to their synthetic equivalents, biopolymers frequently show lower mechanical strength and barrier qualities, requiring modification techniques to improve performance [273, 274].

Technical and financial challenges arise when manufacturing is scaled up from laboratory to industrial scale, especially when it comes to preserving consistent quality and attaining cost-effectiveness. Although recent scientific advancements and rising market demand have started to close the gap, the higher manufacturing costs of biopolymer materials relative to traditional plastics still prevent their broad use [275, 276].

Regulatory factors can present difficulties, particularly when it comes to evaluating the safety of new nanomaterials in applications involving food contact [276]. Access to international markets is complicated by the disparate regulatory systems that various nations maintain for nanomaterials. Another barrier that necessitates open communication on the advantages and safety of nanotechnology in food applications is consumer perception and acceptance [277].

16 Conclusion

This chapter's thorough examination emphasizes how nanotechnology and biopolymer-based composites have revolutionized the food business. Recent developments have shown that these materials provide sustainable and feasible substitutes for traditional packaging, with improved capabilities that go beyond passive containment to include tailored release of bioactive substances, active preservation, and intelligent monitoring.

Materials with better mechanical qualities, barrier functions, and bioactivity than their constituent parts have been produced by combining proteins and polysaccharides to create intricate composite structures. Hybrid systems that include many biopolymers with nanoscale reinforcements including chitosan nanoparticles, cellulose nanocrystals, and graphene derivatives are especially promising. These composites exhibit notable improvements in thermal stability, oxygen barrier qualities,

and tensile strength while preserving biodegradability. Biopolymer composites have transformed food preservation in packaging applications by releasing antibacterial chemicals, scavenging oxygen, or controlling moisture levels. Real-time feedback on food safety and quality is provided by intelligent packaging systems that include gas sensors, time–temperature monitors, and colorimetric indicators. Consumer desires for longer shelf lives, less food waste, and greater openness about product freshness are all directly addressed by these developments. By creating complex delivery methods for bioactive substances, nanotechnology has further increased the potential of biopolymer systems. Lipid–biopolymer hybrid systems and protein–polysaccharide nanoparticles provide previously unheard-of control over the encapsulation, defense, and targeted release of tastes, nutrients, and biopreservatives. These nanoscale technologies get over conventional restrictions on the stability and bioavailability of delicate substances in intricate food matrices. Even with these encouraging advancements, a number of obstacles must be overcome before broad commercial adoption is possible. There are several technological challenges in scaling manufacturing processes while preserving constant quality and performance attributes. Regulatory frameworks are constantly changing, especially with relation to nanoparticles used in food applications, which calls for thorough safety evaluations and uniform testing procedures. Cost factors also continue to be a deterrent to market penetration, however, they are closing as production methods advance and consumer demand for environmentally friendly packaging rises.

The incorporation of stimuli-responsive mechanisms into biopolymer-based composites signifies a groundbreaking advancement in food packaging innovation, allowing unparalleled adaptive functionality that reacts dynamically to environmental conditions and variations in food quality. These sophisticated materials—featuring pH-sensitive polymers, temperature-responsive hydrogels, and light-activated compounds—are developing intelligent systems that may autonomously modify package features to prolong shelf life. Commercial applications are already appearing in high-end food industries, with humidity-responsive packaging that adjusts moisture transfer rates for fresh produce and temperature-sensitive indicators that visually ensure cold chain integrity. The integration of biopolymer science with advanced technologies such as 3D printing and digital fabrication offers customizable, on-demand packaging solutions designed to meet unique product needs. As climate change exacerbates stress on global food systems, these biopolymer composites will be essential for minimizing food waste and tackling plastic pollution—signifying not just a marginal enhancement in packaging materials, but a comprehensive rethinking of how packaging can proactively support sustainable food systems throughout its entire lifecycle, from production to disposal.

Future research goals should concentrate on creating biopolymer composites of the next generation with improved functionality using computational modeling and logical design techniques. Accelerated material development and performance optimization for particular culinary applications are possible through integration with AI and machine learning. Through enhanced recycling, composting, and upcycling pathways, more research into these materials' potential for the circular economy will bolster their sustainability credentials.

Food product packaging, preservation, and delivery are undergoing a paradigm shift as a result of the confluence of biopolymer science, nanotechnology, and smart systems. These technologies will become more and more important in tackling global issues like environmental sustainability, waste reduction, and food security as they develop. Beyond minor enhancements, biopolymer-based composites have the capacity to completely rethink the interaction between food items, packaging, and the customers they are intended for.

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Chapter 13

Recent Advances in Sustainable Biopolymers from Organic Waste and Agro-Based Materials: Food Products and Packaging Applications

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Abstract Conventional plastics, a synthetic polymer derived predominantly from petroleum-based sources, pose one of this era's most environmental challenges. Therefore, steady interest has been concentrated on biopolymers, bio-based carbon materials from renewable natural biomass, as promising eco-friendly and sustainable alternatives. This chapter reviews recent peer-reviewed literature—mainly from 2018 to 2025—on valorizing agro-based residues and organic waste, including lignocellulosic biomass, food waste, and emerging feedstocks such as microbial, algal, and insect-derived polymers into sustainable materials. Biopolymers offer interesting application choices due to their benefits (biodegradability, improved mechanical properties, and antibacterial effects), making them promising sustainable alternatives to petroleum-based plastics. Green synthesis methods, such as enzymatic processes, microbial fermentation, and nanotechnology, further enhance their functionality and environmental performance, aligning with the global development goals. Moreover, active and smart packaging businesses depend on biopolymer—materials that can enhance safety and extend the shelf life of food products. Beyond general industrial use, requiring cross-disciplinary cooperation and supportive legislative frameworks, high production costs, scaling challenges, and legal restrictions are significant barriers to adopting large-scale biopolymers.

Keywords Sustainable biopolymers · Organic waste valorization · Agro-based materials · Renewable feedstocks · Biodegradable food packaging · Circular economy

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Abbreviations

ANN	Artificial Neural Networks
BSF	Black Soldier Fly
CAGR	Compound Annual Growth Rate
DSC	Differential Scanning Calorimetry
EFSA	European Food Safety Authority
FAO	Food and Agriculture Organization
FDA	Food and Drug Administration
FTIR	Fourier-Transform Infrared Spectroscopy
GC–MS	Gas Chromatography–Mass Spectrometry
GHG	GreenHouse Gas
GRAS	Generally Recognized as Safe
HPLC	High Performance Liquid Chromatography
IoT	Internet of Things
ISO	International Organization for Standardization
LA	Lactide acid
LCA	Life Cycle Assessment
LUC	Land-Use change
NMR	Nuclear Magnetic Resonance
PCL	Polycaprolactone
PHAs	Polyhydroxyalkanoates
PHB	Polyhydroxybutyrate
PHBHHx	Poly(3-hydroxybutyrate-co-3-hydroxyhexanoate)
PLA	Polylactic Acid
PBS	Polybutylene Succinate
SCP	Single Cell Protein
SDGs	Sustainable Development Goals
SEM	Scanning Electron Microscopy
SLA	Stereolithography
SLS	Selective laser sintering
TEA	Techno-economic analysis
TEC	Triethyl citrate
TGA	Thermogravimetric Analysis
UV	Ultraviolet
UV-Vis	Ultraviolet-Visible Spectroscopy
XRD	X-ray Diffraction

1 Introduction

1.1 *Biopolymers and Sustainability Overview*

Biopolymers are natural macromolecular substances derived from effective, eco-friendly, renewable biological sources such as plants, animals, and microbial origins [1, 2]. Classification of these polymers is different in literature; they can be classified according to their biological origin, including plants (e.g., cellulose and starch), animals (e.g., chitin, chitosan, and collagen), and microorganisms such as polyhydroxyalkanoates (PHAs) and polylactic acid (PLA), which exhibit industrial scalability [1]. Conventional petroleum-based plastics have persisted in the ecosystem for centuries. On the other hand, bio-based polymers can degrade within a few weeks or months under controlled composting conditions. This biodegradation reduces carbon emissions by up to 60–90% compared to the fossil-based alternatives [1, 2]. Integrating them within circular economy frameworks boosts resource efficiency and increases their relevance to sustainable packaging and biomedical applications [1].

While conventional plastics persist and impact the environment long-term, biopolymers degrade naturally through enzymes and microbes under industrial or natural conditions, producing carbon dioxide, water, and biomass [3]. PHAs and PLA are notable for their degradability via microbial enzymes, which renders them particularly applicable in environmentally friendly packaging and biomedical contexts [4]. They contribute to reducing the environmental burden and limiting long-term plastic waste accumulation, enabling them to enhance material circularity [3]. Furthermore, biopolymers promote sustainability by valorizing organic waste as primary raw materials, reducing reliance on fossil fuels, and supporting a regenerative bioeconomy [5].

Bio-based polymers have been widely explored and are drawing increased interest in food packaging for their environmentally friendly biodegradability, suitable mechanical properties, and proven safety for direct food contact. For instance, PLA, PHAs, and chitosan are commonly employed in developing sustainable food packaging materials.

Common biopolymers, such as PLA, PHAs, and chitosan, are currently excellent examples that can be utilized in food packaging systems. For example, PLA is a biodegradable thermoplastic polyester synthesized through microbial fermentation of lactic acid, which is typically obtained from renewable carbohydrate sources such as corn starch and sugarcane [6]. In addition, PLA has emerged as a promising alternative to traditional single-use plastics in food packaging applications due to its high compostability, favorable mechanical properties, and transparency [1]. Nevertheless, its global adoption is limited by the intense competition over feedstocks with agricultural food production systems. Techno-economic analyses have shown that relying on first-generation feedstocks such as corn grain exacerbates land-use competition, places additional strain on global food supply chains, and may compromise food system resilience.

Alternatively, the high processing costs and underdeveloped supply chain infrastructure still limit second-generation feedstocks such as lignocellulosic biomass (e.g., corn stover) [7]. Addressing such scaling challenges requires proactive policies to diversify feedstocks, encourage agricultural by-product valorization, and promote life cycle-based sustainability assessments for biopolymer production. These actions contribute to integrating biopolymers into circular economy models and promoting the wise use of raw material sources in the biopolymer industry.

Biopolymers comprise 60–100% biogenic carbon derived from renewable biomass, offer sustainable alternatives to petroleum-based plastics, and reduce the overall carbon footprint across the product life cycle [8]. By contrast, synthetic polymers generated from fossil feedstocks are major contributors to greenhouse gas (GHG) emissions; life cycle assessments project CO₂ emissions between 2 and 5 tons for each ton of plastic produced depending on polymer type and manufacturing circumstances [9]. Certain biopolymers, mainly those derived from wood and agricultural biomass, such as cellulose and starch, exhibit a 60–90% reduction in net carbon emissions through naturally closed biogeochemical carbon cycles, as the biogenic CO₂ emitted during degradation is reabsorbed by plants during their next growth cycle [8]. Similarly, alginate and carrageenan, generated from algae, utilize 100% photosynthetic carbon to guarantee their breakdown does not add to net atmospheric CO₂ emissions [10].

At an industrial scale, PHAs and PLA, synthesized from sugarcane and corn starch, exhibit over 80% biogenic carbon content, with life cycle assessments confirming near-net-zero emissions under controlled composting conditions [9]. However, scalability challenges remain, particularly concerning feedstock availability, processing costs, and end-of-life biodegradation variability. While first-generation feedstocks such as corn grain raise land-use competition concerns, second-generation lignocellulosic biomass alternatives, such as corn stover and agricultural residues, remain economically constrained due to higher capital investment requirements and limited supply chain infrastructure. Overcoming these constraints calls for integrated legislative frameworks, incentives for non-food biomass use, and technological developments in biopolymer synthesis to guarantee market competitiveness with usual plastics.

The results highlight the significance of biopolymers for the innovation of material sustainability, aligning with circular economy principles by reducing fossil reliance, enhancing waste valorization, and mitigating long-term climate impacts [8, 9].

Key biopolymers in the food and packaging industries include PLA, PHAs, and chitosan. Derived from renewable resources like sugarcane and corn via microbial fermentation of lactic acid [6]. PLA's compostability and mechanical properties make it an ideal alternative to single-use plastics in food packaging [1]. However, persistent feedstock competition between biopolymer production and nutritional agriculture remains a critical barrier to sustainable scaling, as evidenced by system-scale techno-economic analyses [7]. Recent life cycle studies draw attention to unavoidable land use distribution and resource prioritization issues when using first-generation agricultural feedstocks, thus highlighting the need for focused non-food biomass valorization pathways to achieve meaningful circularity in bioplastic ecosystems.

Biopolymers are gaining recognition for their role in sustainable materials. Nanotechnology and biopolymer composite engineering have significantly enhanced these materials' mechanical, thermal, and barrier qualities, increasing their competitiveness with petroleum-based plastics in numerous industrial applications [11, 12]. However, further research is needed to optimize starch-based biopolymers for large-scale use in compostable packaging, particularly concerning moisture resistance and mechanical durability.

Although biopolymers hold remarkable transformative potential, their large-scale implementation is hindered by several barriers, notably high production costs, limited scalability, and strict regulatory frameworks. Overcoming these barriers requires a comprehensive and collaborative approach that integrates sustainable feedstocks, the development of innovative processing technologies, and the implementation of supportive policy measures. The continued reliance on first-generation agricultural products such as maize starch remains the predominant source of biopolymer production. However, their overlap with food supply chains raises notable sustainability concerns. Therefore, second and third-generation alternatives—particularly ligno-cellulosic biomass and organic waste—are being explored to determine biopolymer synthesis's economic and environmental feasibility [5, 13].

Recent advancements in genetic engineering and microbial fermentation have increased biopolymer production while reducing reliance on costly raw materials. Wider industrial adoption of bio-based polymers requires regulatory systems that ensure compliance with sustainability standards outlined in international frameworks such as ISO. Additionally, using nanofillers and composite reinforcements helps enhance the physicochemical properties of biopolymers, thereby improving their competitiveness with fossil-based plastics [5, 13].

Through ongoing research and cross-sector collaboration, biopolymers have the potential to reduce plastic pollution significantly, promote circular economic concepts, and contribute to the improvement of sustainable material innovations [1].

Given the growing demand for sustainable materials, investigating the environmental impact of biopolymers is becoming increasingly essential. Their contribution to sustainability is reflected in their ability to reduce greenhouse gas emissions, decrease plastic pollution, and enhance waste valorization—a topic further explored in the following section.

1.2 Sustainability Impact

Biopolymers effectively solve environmental problems associated with plastic waste and greenhouse gas emissions, mitigating their harmful effects. Several studies have indicated that the advantages of biodegradable alternatives, such as PLA or PHAs, contribute to reducing carbon footprints and plastic pollution in marine environments [1, 4]. They support the circular economy concept due to using agricultural waste and cellulosic biomass as sustainable raw materials in manufacturing. This decreases waste, enhances resource efficiency, and increases products' value from organic

waste streams. Therefore, this approach is exhibited as a sustainable model [1, 14]. Under specific conditions, the biodegradability feature of biopolymers ensures their decomposition into eco-friendly by-products such as carbon dioxide, water, and biomass, further reducing their environmental impact [14].

Global sustainability initiatives are strongly aligned with the adoption of biopolymers, particularly the United Nations' Sustainable Development Goals (SDGs), which emphasize the importance of environmentally responsible industrial practices by reducing dependency on finite fossil resources and enabling sustainable material cycles. The reliance on biopolymer technologies intersects with several Sustainable Development Goals. For example, we see this clearly in SDG 12, the responsible consumption and production, as well as the climate action goal, as SDG 13, due to adopting practices based on them contributes to reducing greenhouse gas emissions and shifting industries toward climate-friendly alternatives. Furthermore, by reducing the long-term environmental burden of synthetic polymers, their ability to replace persistent plastic pollutants in marine environments also directly enhances the SDG 14, life below water goal [14].

Sustainable materials have significantly increased, driven by the growing consumer awareness and the regulatory pressure regarding plastic waste reduction; this promotes biopolymers as a crucial response to several industries, including packaging, agriculture, and healthcare [2, 3]. The recent forecasts of the global biopolymer and bioplastic market, valued at USD 14.3 billion in 2023, are projected to grow at a 15.2% compound annual growth rate (CAGR), reaching USD 38.5 billion by 2030. It is worth noting that advancements in biotechnology, environmental policies, and increasing bio-based substitute use in the industry drive this significant growth [2].

However, further developments in scalable processing methods, enhancing the performance of materials, and strengthening collaboration of legislators and businesses are essential to fully harnessing the potential of biopolymers. While addressing economic and manufacturing issues, this approach will create new pathways for biopolymers and increase their viability as a potential substitute for traditional plastics in a circular bioeconomy [2].

The history of sectors formerly dependent on conventional plastics is transitioning toward sustainable materials. The food and packaging sectors propel biopolymer utilization owing to customer demand for sustainable alternatives, stringent regulations, and improved material efficacy. This section will analyze the impact of biopolymers on various industries, presenting a viable and sustainable method for mitigating plastic waste and promoting circular economic principles.

1.3 Biopolymers in Food and Packaging Industries

About 40% of the global plastic waste comes from food and packaging industries; this makes them major contributors to plastic consumption. For instance, single-use plastics prevalence in this sector is based on their cost-effectiveness, durability, and versatility. On the other hand, their persistence in ecosystems has led to severe

environmental issues, including the proliferation of microplastic and long-term environmental degradation. In response, bioplastics enter the competition as a viable and sustainable alternative, offering comparable mechanical strength, barrier functionalities, and thermal stability while being biodegradable and significantly reducing environmental impact [15–17].

To provide a clear comparative overview of biopolymers frequently utilized in sustainable food packaging, Table 1 summarizes their source materials, mechanical and barrier properties, biodegradability profiles, processing challenges, and relative economic considerations. This summary is a reference point for the detailed discussions of each biopolymer type presented in this section.

The global biopolymer and bioplastics market was estimated to be worth approximately USD 14.3 billion in 2023, with projections indicating a growth to USD 38.5 billion by 2030, corresponding to a notable compound annual growth rate (CAGR) of 15.2% [2]. Technological advancements in biopolymer production, sustainability policy initiatives, and rising consumer demand for eco-friendly materials drive the market expansion. Due to the growing environmental concerns, many worldwide governments have developed regulations to reduce reliance on petroleum-based plastics. These measures are helping to accelerate the shift toward biopolymers, particularly in sectors like packaging, agriculture, and healthcare. At the same time, adding nanoparticles to biopolymers has proven effective in enhancing their strength and barrier properties, opening up new opportunities for their use in advanced applications such as smart packaging and medical technologies [2].

To overcome the challenges of the biopolymer industry to widespread adoption through advanced processing technologies and strategic collaboration between industry stakeholders and policymakers [11, 15]. This transition is essential for reducing plastic waste, fostering circular economy models, and advancing sustainable material innovation [11, 15]. For example, packaging based on PLA and films derived from starch can replace wrappers from traditional plastic, and chitosan films show antimicrobial barrier characteristics in the food industry. Continuous improvement efforts also provide practical solutions for packaging applications in the food industry, where biocomposites reinforced with natural fibers are developed to enhance mechanical durability and biodegradability [11, 38]. These activities could align with the consumer's demands for sustainable alternatives and the industry's efforts to comply with developed regulations as sustainable goals for reducing plastic pollution [15, 38].

In addition to sustainable packaging solutions, biopolymers contribute to transforming organic waste management and reusing. Integrating them into circular economy models enables industries to transform waste into high-value materials, minimizing environmental impact and improving resource efficiency. In the following section, the role of biopolymers in waste valorization and circular economy strategies will be examined.

Table 1 Comparative analysis of key biopolymers used in food packaging: source materials, tensile strength, barrier properties, biodegradability, processing challenges, and relative cost

Biopolymer type	Tensile strength (MPa)	Barrier properties	Cost (\$/kg)	Degradability	Processing challenges	Sources
PLA	35–65 MPa	Moderate oxygen barrier, weak to moisture	~\$2.5–\$3.5/kg	Slow degradation due to semicrystalline structure; requires high-temperature industrial composting	Processing temperature: 160–230 °C; degradation starts at ~200 °C due to thermal sensitivity	[6, 7, 9, 18, 19]
PHAs	General PHA range (including PHBV, medium-chain-length-PHA): 1–40 MPa (varies by type)	Superior oxygen barrier and moderate water resistance, (improves with higher crystallin)	~\$8/kg, with variations depending on application (e.g., \$7.6/kg for packaging, \$11.9/kg for biomedical use)	Biodegradable in soil and water PHAs, including PHBHHx, show good biodegradation properties in both soil and seawater	High production cost because of expensive feedstock materials and complex downstream processing	[11, 20–25]
Starch-based	5–6 MPa	Poor moisture resistance and mechanical stability require blending for improved barrier properties	EUR 2.5 to EUR 4 per kg (~\$2.7–\$4.3 per kg)	Compostable and highly biodegradable—quickly breaks down in moist conditions; modification can slow the process	Highly sensitive to water and mechanical Limitations. Requires blending, chemical modifications, or reinforcements to improve durability and processability	[9, 11, 26–29]

(continued)

Table 1 (continued)

Biopolymer type	Tensile strength (MPa)	Barrier properties	Cost (\$/kg)	Degradability	Processing challenges	Sources
Chitosan	15–44 MPa (this varies by source and processing, with higher values found in chitosan from insect sources)	Strong oxygen barrier with moderate water vapor permeability, enhanced by additives. Composites improve UV resistance and strength	\$8.39–\$14/kg, depending on production scale and region. Larger-scale production reduces costs	Biodegradable, non-toxic, and enzymatically degradable with a degradation rate influenced by molecular weight, deacetylation degree, and other environmental factors	High production cost, energy-intensive extraction, and low yield (20.85%). Appropriate management of chemical waste is crucial to reduce environmental impact, including poor mechanical properties and water sensitivity restricting its applications	[9, 15, 26, 27, 30–33]
Lignocellulosic	88–1500 MPa, depending on fiber type and reinforcement. Flax, hemp, jute, and sisal exhibit high strength, with nanocellulose and lignin improving mechanical performance	Strong oxygen barrier because of cellulose crystallinity and lignin. High water vapor permeability, reducible with nanocellulose coatings and surface modifications	Feedstock cost ~\$0.06–\$0.15/kg, total production cost estimated at \$1.13–\$1.97/kg, influenced by processing efficiency and fixed costs	Highly biodegradable; decomposed within months to a few years via microbial and enzymatic breakdown. Composting accelerates degradation (C/N 25–30:1, moisture 50–60%, aeration required)	Requires intensive preprocessing (hydrolysis, steam explosion). High cost, variable properties, and lower thermal/mechanical stability than synthetics	[7, 9, 27, 29, 34–37]

1.4 Waste Valorization and Circular Economy

Biopolymers possess inherently sustainable properties as they rely on the wise conversion of organic waste resources to enhance the environment and the economy. This makes them compatible with the principles of the circular economy by converting organic waste into high-value materials [39], contributing to the optimal utilization of environmental resources. In contrast to relying on limited fossil resources in conventional plastics, natural resources enhance manufacturing by applying biopolymers from renewable raw materials such as agricultural waste, food processing by-products, and cellulosic biomass [5, 39], which reduces reliance on non-renewable resources and precisely the advocates of the global sustainability initiatives [5, 39].

Sugarcane bagasse, a by-product of sugar production, is a substrate for microbial fermentation to produce lactic acid, a precursor to PLA, a compostable biopolymer widely utilized in food packaging [5]. The valorization of sugarcane bagasse into biopolymers is a critical advancement in sustainable material development, offering an economically viable alternative to petroleum-based plastics [40]. In addition, starch-based bioplastics extracted from potato peels provide an environmentally friendly alternative to single-use plastics [5]. According to several studies, optimizing the mechanical properties of these starch-based bioplastics through modifications such as plasticization could enhance their applications in the food sector (packaging) and industry [5]. Research continues to focus on improving the exploitation of corn stover as a biopolymer source; however, it and its husks contribute vitally to the valorization of lignocellulosic biomass. Its direct application as a starch-based bioplastic remains less common and less documented in scientific literature [5]. Furthermore, waste valorization strategies can be enhanced using specific bacterial strains, such as *Cupriavidus necator* and *Pseudomonas putida*, which to be utilized for microbial fermentation processes to produce PHAs as a class of biodegradable polyesters [4]. These strategies may be further enhanced by applying genetic engineering and fermentation process innovations to improve PHA synthesis further, expanding its economic viability and enhancing its application in sustainable biopolymer production [40].

Transforming organic waste into valuable materials via biopolymer processes enhances resource efficiency and supports environmental sustainability by reintegrating them into natural biodegradation cycles [3]. PLA and PHAs, compared to materials from conventional plastic sources, play a significant role in promoting the circular economy and improving environmental sustainability by relying on extraction processes from renewable sources designed to be degraded under appropriate conditions, reducing waste accumulation and fostering a circular economy [11]. Due to relying on sustainable sources, these materials significantly reduce carbon footprints and reduce the potential for plastic pollution in nature while maintaining functional performance in various industrial applications [5]. The widespread adoption

of biopolymers aligns with the SDGs, particularly SDG 12, which advocates responsible consumption and production by promoting sustainable material use, reducing waste generation, and supporting eco-innovation [40].

Despite the dependency of biopolymers on the circular economy as promising solutions for reducing the environmental footprint and enhancing resource sustainability, the conditions for their adoption and application across a wide range of sectors depend on factors such as the availability of regional technological capabilities, regulatory frameworks, and market demands.

1.5 Global Importance of Biopolymer Innovations

The scientific adoption of biopolymers has increased due to their promising potential as sustainable and biodegradable alternatives to conventional plastics in industrial applications. Market analysis shows a significant growth in the adoption of biopolymers, and forecasts indicate that by 2025, the global market value will rise at a CAGR of 21.7%, from US\$10.5 billion in 2020 to US\$27.9 billion [13]. Despite challenges such as competition between renewable feedstocks for biopolymer production and food needs, biopolymers are now being produced on an industrial scale, further enhancing their growing role in sustainable manufacturing [13, 40].

Biopolymers are widely recognized as replacements for conventional plastics. Unlike fossil-based polymers, which contribute significantly to solid waste accumulation, biodegradable biopolymers are expected to reduce environmental pollution while promoting sustainable resource cycles [41]. Additionally, life cycle assessments suggest that biopolymers divert waste from landfills—where approximately 80% of petroleum-derived plastics remain non-degradable and offer a lower carbon footprint due to their renewable feedstocks [13].

Additionally, increasing biopolymers' economic viability is another credit that further reinforces the sustainability and biodegradability. For instance, recent advancements in biodegradable polymers indicate that both are cost-competitive and exhibit mechanical properties comparable to traditional plastics, enhancing their feasibility for widespread adoption [42]. Moreover, biopolymers can degraded naturally without residual persistent accumulation of microplastics or toxic is essential in tackling the global plastic waste crisis [41].

It has been noticed that there is a steady shift to biopolymer-based solutions for global industries across multiple sectors, driven by the sustainable alternatives biopolymers provide to traditional plastics. PLA-based bioplastics are widely used in food and beverage packaging for their biodegradability, renewability, and superior barrier properties compared to petroleum-derived polymers [39, 41]. Due to its functional properties, chitosan-derived coatings have gained more attention globally as coating agents in food preservation systems. Chitosan coatings are known for their antimicrobial properties and film-forming abilities. For such reason, they are used as preservatives for extending food shelf life, minimizing waste, and serving as edible coatings for marine products.

Additionally, it is an effective antimicrobial and antioxidant agent in seafood products [43]. Biopolymers are also used in the automotive sector. For example, Toyota employs PLA composites based on agro-materials for lightweight, sustainable components, improving fuel efficiency, and reducing environmental impact [1, 11].

Biopolymers improve sustainability and green manufacturing innovation, thus playing a key role in industrial integration. Despite significant advancements in biopolymer technologies, several challenges persist. One of the primary obstacles is scaling up production technologies to meet global demand while maintaining cost-effectiveness. While novel extraction and processing techniques have improved efficiency, many biopolymer production methods remain resource-intensive and economically unfeasible for large-scale implementation [40].

Their enhancement under diverse environmental conditions significantly influences the widespread adoption of biopolymers. For example, biopolymers must improve their mechanical strength, thermal resistance, and biodegradability, as their stability and durability are influenced by several factors, including chemical composition, molecular structure, and environmental exposure [3].

Research collaborations and investment in advanced processing methods are needed to overcome these limitations. For example, combining nanotechnology and genetic engineering (e.g., carbon nanotubes and graphene) has demonstrated significant potential to improve biopolymers' mechanical and thermal properties [13]. Furthermore, highlighting the importance of interdisciplinary collaborations between scientific institutions, industry stakeholders, and regulatory agencies is vital to bridging the gap between laboratory innovations and commercial adoption [40]. Biopolymers have gained the potential to transform from a niche use case to mainstream sustainable materials due to leveraging technological advancements and fostering global cooperation, which has driven the shift toward a circular bio-economy. Moreover, they offer transformative opportunities to create sustainable food systems and foster innovation in material science through bridging technological advancements with practical applications.

Due to the growing recognition of biopolymers' pivotal roles in the industry and their impact on policymakers, there is an urgent need to explore biopolymers' development, diverse applications, and potential sustainability implications more deeply. With the growing recognition of the pivotal roles played by biopolymers in industry and policymakers, this chapter identifies key objectives for the latest discoveries, innovative uses, and promising future of biopolymers, particularly in the food and packaging industries.

1.6 Objectives

This chapter offers an in-depth review of the advanced biopolymers and their innovative applications, emphasizing their crucial part in promoting sustainable materials

across various global sectors. Focusing on their innovative applications in sustainable food items and packaging, we will also discuss how they assist the transforming potential by drawing their supplies from organic waste and agricultural feedstocks.

The first goal is to critically evaluate recent technologies and innovations in advanced biopolymer methodologies (e.g., microbial fermentation, enzymatic hydrolysis, green chemistry, and nanotechnology) and how these techniques can improve their functional, mechanical, and environmental performance, making them viable alternatives to conventional petroleum-based plastics. For example, important advances proceeding the industry forward will be highlighted, including those in genetically engineered microbial strains and nanocellulose reinforcement.

The next part highlights the sustainable practices of biopolymers and their applications in food industries, such as biodegradable packaging, food preservation, and edible coatings. This will mainly consider their advantages in biodegradability, barrier qualities, and antibacterial function, as well as their capacity to satisfy industrial needs and regulatory sustainability standards while supporting world food safety and waste reduction initiatives.

A third primary goal is examining the commercial scalability and economic viability of using biopolymers on a wide scale. This involves carefully reviewing several views on market trends, production costs, regulatory frameworks, and integration problems. The investigation will provide viable ways to increase efficiency, address these challenges, and seamlessly integrate biopolymers into present industrial supply chains.

The chapter also investigates creative biopolymer feedstocks from new sources, including microbial biosynthesis, insect-derived polymers (e.g., chitosan from black soldier fly larvae), and agricultural by-products (e.g., lignocellulosic biomass from crop leftovers). It emphasizes these substitutes as sustainable routes that can lessen environmental effects, minimize resource rivalry, and decrease reliance on conventional agricultural supplies.

Finally, the discussion will include how recent trends based on biopolymer applications fit into the global sustainability framework through the concept of the circular economy and the vital roles they play in enhancing resource efficiency by valorizing organic waste from sustainable sources. The discussion will also cover the positive impact of reducing plastic pollution and greenhouse gas emissions and promising intersections in supporting sustainable development goals through the global adoption of innovation in these technologies. It will also present analyses and policy proposals that will support the integration of biopolymers into industrial sectors and accelerate their adoption, particularly in the food and packaging industries.

This chapter addresses these objectives and provides a logical, forward-looking perspective for researchers and politicians committed to advancing sustainability through biopolymer development. It highlights the need for interdisciplinary cooperation and geographical factors to reach these objectives, so it is important to ensure that biopolymer solutions are locally flexible and internationally important.

2 Sources of Biopolymers

2.1 *Introduction to Biopolymer Feedstocks*

Biopolymers, synthesized from renewable biological feedstocks [4, 44], represent a significant innovation in sustainable material science [40], providing viable alternatives to fossil-based plastics [4, 44]. While addressing pressing global challenges such as waste accumulation [40] and climate change [32]. Unlike conventional polymers, which rely on finite fossil-based resources, biopolymers originate from biologically renewable sources, facilitating lower carbon footprints, enhanced biodegradability, and integration into circular economy models [23, 44]. However, the diverse nature of biopolymer feedstock spanning organic waste, agro-based materials, marine and desert plants, insect-derived polymers, and microbial systems necessitates a systematic classification framework to evaluate their sustainability, industrial feasibility, and economic trade-offs.

Biopolymer feedstocks can be categorized into five primary groups based on their origin: organic waste, agro-based materials, microorganisms, algae, and insects. These feedstocks are often further classified into first-, second-, and third-generation categories based on their source and sustainability characteristics (see Sect. 13.2.3.2 for a detailed classification).

In addition to the generational classification addressed in Sect. 13.2.3.2, biopolymer feedstocks can also be grouped thematically based on their biological origin, as outlined below:

i. **Organic Waste**

Agricultural residues, food processing by-products, and plant-based waste streams can be upcycled into cellulose, starch, and lignin-based biopolymers [40, 44, 45]. Current estimates suggest that significant quantities of global agricultural residues are converted into cellulose for biopolymer applications annually. This process significantly contributes to landfill waste reduction and methane emission mitigation, though precise reduction impacts vary based on regional waste processing methods and feedstock types [15, 40, 45].

ii. **Agro-Based Materials**

Starch-rich crops such as corn and sugarcane are widely used for PLA production [7, 41]. However, their extensive utilization presents challenges related to land-use competition and food system sustainability, necessitating the exploration of alternative non-food-based feedstocks [7]. (See Sects. 13.2.3.3 and 13.2.3.8 for related feedstock classifications and environmental impacts.)

iii. **Biopolymers from Marine and Desert Plants**

Marine-derived polysaccharides like chitosan exhibit moisture-resistant and film-forming properties, making them valuable for sustainable material applications [46]. Similarly, prickly pear mucilage, a desert-derived biopolymer, has been optimized

for edible film development, demonstrating strong potential for packaging applications [47]. However, large-scale industrial adoption faces significant challenges, mainly due to high-energy processing demands and seasonal variability in raw material supply [26]. While cost estimates remain variable across studies, biopolymer processing is generally more resource-intensive than conventional synthetic plastics derived from petroleum [26].

iv. **Insect-Derived Polymers**

Insects serve as a sustainable and efficient feedstock for biopolymer production. In particular, insect-derived chitosan has emerged as a promising material due to its biodegradability, functional activity, and potential applications in packaging, biomedical fields, and environmental remediation. (For technical processing challenges and extraction methods, see Sect. 13.2.5.2.)

v. **Microbial Biopolymers**

Bacterial fermentation enables the synthesis of high-performance biodegradable polymers, such as PHAs. These materials exhibit remarkable biodegradability and structural tunability, making them a viable alternative to fossil-based plastics [4]. However, their economic feasibility remains constrained by high fermentation costs and the need for optimized substrate selection [7]. The production cost of PHB is significantly influenced by carbon source selection and process conditions, often making it 4 to 10 times more expensive than conventional polyethylene [4]. While innovative strategies such as utilizing agro-industrial residues have demonstrated potential for cost reduction, further advancements in feedstock utilization and bioprocess efficiency are necessary to enhance commercial scalability [15, 23].

Industries and governments explored many investigations on biopolymer innovation. In this sense, a comprehensive valuation framework including central sustainability like biodegradability, life cycle assessment, and either they be included on the circular economy conception were well examined. In addition, researchers and companies focused to establish and conceive novel, innovative, eco-friendly materials. It is a crucial step to attain global initiatives such as the European Green Deal and the SDGs, which (i) highlight a reduction of fossil-fuel-derived plastics and (ii) approve bio-based alternatives materials [3, 23].

2.2 *Organic Waste*

The recycling of organic waste into biopolymers constitutes a progression in main-tenable material. As an illustration, crop residues, agri-foodstuffs, and post-use organic waste have occurred as talented raw materials for biopolymer creation [40]. As a model, proteins, cellulose, pectin, lignin, and lipids could be employed as a proper source for biopolymers in food packaging [45].

2.2.1 Food Processing Residues

Food processing industry waste, comprised fruit and vegetables peels and seeds, are abundant in polysaccharides, starch, and pectin. These substances are brilliant candidates for biopolymer manufacture [2]. Developed from plant sources, bioplastics from starch have been successfully established [48]. By microbiological and enzymatic treatments, these processing wastes could be recovered into PLA and PHAs [49].

2.2.2 Municipal Organic Waste

Progressive biotechnological developments viz. microbial and fermentation bioconversion have revealed a good tool to transform municipal organic waste on valuable biopolymers products like PHAs and PHB. Microbial networks could generate PHB levels of equal to 0.9 g/L, improving the waste managing, lessening requirements on fossil-based polymers, and assisting to the circular economy [50].

2.2.3 Processing and Extraction Techniques

In order to enhance the polymer quantity/quality, it is crucial to apply innovative extraction techs. For example, enzymatic hydrolysis could decompose waste, rich on complex sugars, to fermentable simple sugars. In the case of lignocellulosic biomass, this expertise is operative to produce (PHAs) and polylactic acid (PLA) as biopolymer [49, 51, 52]. By using low-cost feedstocks like whey permeate or molasses, *Pseudomonas aeruginosa* and *Cupriavidus necator* could accumulate PHAs [53], and PLA was synthesized by *Lactobacillus* strains [53].

Enzymatic hydrolysis driven by cellulases and hemicelluloses markedly improves the conversion of lignocellulosic biomass, releasing monosaccharides that act as feedstock for producing PHA, PLA, and other bio-based polyesters [45].

In order to recover pectin and chitin, respectively, from fruit peels and seafood waste, acid and alkaline treatments were employed. Acid hydrolysis could enhance the film-forming capacity of citrus peel pectin, which was a valuable material for biodegradable packaging [54]. On the other hand, alkaline treatments could assist the extraction of chitin from crustacean shells [54].

2.2.4 Environmental and Economic Benefits

Turning farm and food waste into biopolymers is a considerable environmental advantage. It sharply reduces the potential environmental impact by decreasing landfill waste and easing pressure on the climate. When those recovered feedstocks are converted into biodegradable plastics such as PLA or PHAs, they stand in for oil-based polymers, trimming greenhouse-gas footprints and advancing

global climate goals; this waste-to-biopolymer pathway helps phase out fossil-fuel dependence while ticking multiple boxes for sustainability [18].

Valorizing organic waste into biopolymers boosts resource efficiency and underpins sustainable manufacturing. Transforming discarded streams into high-value polymers embeds circular economy thinking and lessens dependence on fossil-derived plastics. It also supplies low-cost feedstocks, sparks green innovation, and opens fresh business prospects for the bio-based sector, strengthening economic and environmental sustainability over the long term [48].

2.2.5 Economic Feasibility and Life Cycle Analysis

Although organic-waste biopolymers offer clear environmental gains, scale-up is still hampered by economic and logistical hurdles. Life-cycle costing studies show that swapping first-generation feedstocks (such as corn and sugarcane) for agro-industrial residues can trim production costs by roughly 40–50%—but only if process efficiencies are pushed to their optimum [40]. Even so, inconsistent feedstock supply, inadequate infrastructure, and the hefty upfront outlay for fermentation and enzymatic hydrolysis units remain major roadblocks to commercial expansion [7].

A life cycle assessment (LCA) conducted on biopolymer production from food waste suggests a significant reduction in greenhouse gas emissions, fossil fuel consumption, and water usage compared to traditional petrochemical plastics [3]. However, industrial-scale implementation remains constrained by the inconsistent availability of organic waste streams, requiring integrated supply chain solutions and regional waste management policies to support stable production [45].

2.2.6 Challenges and Future Outlook

Turning organic waste into biopolymers will not scale until a few stubborn obstacles are cleared. The biggest is the feedstock itself: volumes swing with the seasons and arrive in scattered pockets, throwing supply chains off balance. To cope, producers need tight, well-timed systems for collecting, pre-processing, and storing the material [45]. Cost of treatment and technological limits persist a serious block, since fermentation and enzymatic hydrolysis are quiet among the costliest stages. In addition, severe monitoring and market hurdling must be stunned before biopolymers generated from food waste [3]. Progress in biopolymer development will benefit from integrated biorefinery models that valorize diverse biomass streams and the continued application of green chemistry principles and nanoscale engineering. Moreover, nanotechnology and green chemistry advancements offer promising avenues for enhancing organic waste-based biopolymers' mechanical and barrier properties, expanding their applications beyond food packaging into medical, agricultural, and industrial sectors [40].

2.3 *Agro-Based Materials*

Crops such as corn, sugarcane, and soybeans have become key raw materials for producing bioplastics. Because of the renewability feature they own and are easy to source, they are represented as a practical, eco-friendly alternative to petroleum-based inputs. Farmers cultivate these plants mainly for the sugars, starches, and oils they contain, which chemists turn into high-performance biopolymers. Using plant-based feedstocks helps the industry cut its dependence on fossil resources and move toward more sustainable manufacturing.

Agro-based materials refer to renewable resources derived from agriculture, such as crops and their residues, which serve as feedstocks for biopolymer production. Unlike petroleum-based raw materials, these resources grow yearly, making them ideal for a circular, sustainable economy. Farmers supply a range of starting materials: starch-packed crops like corn, potatoes, and wheat; sugary crops such as sugarcane and sugar beet; and oily seeds like soybeans [52]. Biological resources, including carbohydrates, sugars, oils, and proteins, are essential for producing a variety of biodegradable polymers [9, 10]. For instance, corn grain and sugarcane juice are significant sources of fermentable sugars for manufacturing bio-polyesters like PLA [55, 56]. Similarly, soybean-derived compounds, such as oil and protein, produce biopolymer resins and protein-based plastics [10, 45].

The appeal of agro-based feedstock lies in their prospective to reduce dependency on fossil fuels and lower the environmental footprint of plastics production [52]. However, using edible crops for plastics has increased concerns about food security and land use, leading to a distinction between different “generations” of feedstocks and a push toward utilizing agricultural by-products and wastes for polymer production [45, 55]. Crop leftovers—cereal straws, onion skins, and other food-processing scraps—are now seen as promising biopolymer feedstocks, providing a greener option than first-generation crops [45]. By upgrading these by-products, manufacturers reduce competition with the food supply and advance a circular economy that turns waste into valuable raw materials [7, 52].

Progress aside, the bioplastics sector still has hurdles—namely, cost competitiveness, the ability to scale up production technology, and proper end-of-life handling—before plant-based feedstocks can reach their full promise [55, 56]. A key obstacle is price; bioplastics generally cost more than petroleum-based plastics because large-scale facilities are still limited, and crude oil remains relatively cheap, slowing mass adoption [55]. On top of the cost issue, bioplastic production tends to be less energy-efficient and brings added environmental impacts from the farming stage, both of which slow down large-scale expansion [55]. End-of-life handling is another sticking point; dedicated recycling channels for most bioplastics are still lacking, and many consumers remain unsure about how to dispose of these materials [55]. LCAs have revealed that incineration or landfilling of bioplastic products is not a viable solution, emphasizing the need for improved waste management strategies [56]. Furthermore, reducing greenhouse gas emissions must reach zero land-use change (LUC) emissions to ensure the sustainability of bioplastic waste management [56].

Addressing these challenges is crucial for the future of agro-based feedstocks in the bioplastics industry.

Key considerations in adopting agro-materials include their availability, cost, and conversion efficiency into polymers. Agricultural residues like wheat straw, rice husks, and sugarcane bagasse have been explored as viable sources for polymer synthesis [20, 52]. For instance, sugarcane bagasse, a by-product of sugarcane processing, contains 32–48% cellulose, 25–32% hemicellulose, and 19–24% lignin, making it a promising feedstock for biopolymer production [40]. Similarly, wheat straw comprises 31.10% hemicellulose, 40.67% cellulose, and 11.7% lignin, which can be efficiently converted into biopolymers through advanced pre-treatment and conversion technologies [40]. By leveraging these non-food biomass sources, bio-based polymers' environmental and economic feasibility can be further improved, contributing to a more sustainable material economy [40, 52]. For instance, agricultural residues valorization could reduce greenhouse gas emissions [52]. Furthermore, fulfilling circular economic performs in agricultural systems improves resource effectiveness and decreases material losses [52].

2.3.1 Agricultural Residues

For biopolymer fabrication, agricultural excesses are among the commonly obtainable sources of organic waste. To produce PLA, cellulose, hemicellulose, lignin, and sugarcane bagasse, are lengthily employed [51]. Similarly, wheat straw and corn husks are frequently converted into fermentable sugars, which serve as precursors for microbial fermentation to produce PHAs. These agricultural by-products reduce waste and enhance resource efficiency by supporting sustainable biopolymer production [26, 50].

Given the wide availability of agricultural residues, understanding their classification based on their origin and processing requirements is crucial for optimizing their use in biopolymer production.

2.3.2 Role of Agro-Based Feedstocks in Sustainable Biopolymer Production

The impacts of biopolymers on human health and the environment depend on the type of feedstock used for biopolymer production. The feedstocks are divided into three generations: first, second, and third [57].

First-generation feedstocks are carbohydrate-rich materials (corn, wheat, sugarcane, sugar beet, potato, plant oils, and others) that serve as food and biofuel sources. Second-generation feedstocks include non-food crops (e.g., cellulosic biomass from switchgrass) and by-products of first-generation crops, such as corn stover and sugarcane bagasse. Third-generation feedstocks consist of biomass obtained from industrial or municipal waste streams, algal biomass, and other food-industry by-products [57].

First-generation feedstocks generally pose minimal direct health risks when used in biopolymer production (since they are edible), but their large-scale cultivation has significant environmental consequences. Expanding first-generation feedstocks, such as sugarcane and corn, increases land-use demand, disrupts ecosystems, and threatens ecological balance due to deforestation and shifts in agricultural priorities. Similar concerns have been raised in biofuels, where large-scale crop diversion has led to environmental degradation and rising food prices [58]. Second-generation feedstocks, primarily consisting of residues or dedicated non-food crops, present a more ethically viable and widely available alternative by avoiding food vs. fuel conflicts and significant health concerns. However, despite these advantages, their utilization often necessitates additional pretreatment steps to release fermentable sugars, leading to increased processing complexity. These feedstocks need refined handling tools and high costs. The overall economic practicability of expanding second-generation feedstocks mainly counts on technical progressions [55]. However, both first- and second-generation agriculture depend on fertilizers, pesticides, and herbicides, which cause and adverse health impact and ecological contamination. In dissimilarity, third-generation feedstocks do not necessitate intensive farming inputs [56].

Resulting from residues and crops, agro-based materials attend as an appreciated feedstocks for biopolymer production [56].

However, if these materials originate from polluted environments, they may contain contaminants like heavy metals or other pollutants, necessitating complex purification methods, depending on contamination levels and available technologies.

Resulting from residues and crops, agro-based materials attend as an appreciated feedstocks for biopolymer production [59]. These materials can be processed into biodegradable biopolymers, including PHA and PLA, offering an alternative to synthetic plastics [60]. Unlike petroleum-based plastics, certain biopolymers exhibit biodegradability, depending on their chemical structure and environmental conditions, contributing to sustainable waste management strategies [61]. While biopolymers derived from renewable feedstocks have sustainability benefits, their environmental impact varies depending on processing techniques, life cycle stages, and disposal methods [61]. The carbon cycle can be maintained in a closed-loop system by sourcing carbon from agricultural biomass, including lignocellulosic materials. CO₂ fixed by crops is released upon biodegradation, contributing to sustainable carbon management and mitigating long-term emissions [62].

The agro-industry already produces vast amounts of biomass, including dedicated crops and processing by-products, which can serve as raw bioplastic materials [63]. Utilizing these resources for materials adds value to agricultural produce and waste, aligning with circular economic goals. For example, agricultural residues like stalks, husks, straws, bagasse, and peels, which were traditionally treated as waste, are now considered valuable resources that can be converted into bio-based products such as bioplastics [64]. This reduces pollution and waste disposal issues and decreases reliance on finite fossil fuels by replacing them with bio-based, renewable alternatives [65]. However, realizing these benefits requires carefully selecting feedstocks and efficient processing technologies.

Corn is dominant among the most widely used first-generation feedstocks due to its high starch content and well-established fermentation processes for producing biopolymers such as PLA.

2.3.3 Corn-Based Biopolymers

Corn starch derived from *Zea mays* (maize), a globally cultivated cereal, is an important renewable feedstock for biopolymer production, specifically PLA. PLA is produced through the fermentation of starches like corn, which are abundant and competitively priced due to emerging industrial production technologies [66, 67]. The economic viability of PLA production is enhanced by its production from agricultural by-products, mainly carbohydrate-rich resources [67], making it a preferable choice in the biopolymer sector. Converting corn starch into PLA involves a multi-step biochemical process. First, the starch is subjected to enzymatic hydrolysis (typically using amylase enzymes) to break it down into fermentable sugars, primarily glucose [51].

Corn starch is one of the most widely used feedstocks for biopolymer synthesis, particularly for the production of PLA. The enzymatic hydrolysis of corn starch produces glucose, which is fermented into lactic acid, the precursor for PLA. PLA is extensively used in packaging, disposable utensils, and biomedical applications due to its biodegradability and mechanical properties [51]. Recent advancements in process optimization have improved the efficiency and cost-effectiveness of converting corn starch into PLA, making it a leading biopolymer in global markets [68].

Similar to corn, sugarcane serves as another significant feedstock for biopolymer production, particularly in tropical regions where sugar-based bioplastics are gaining traction.

2.3.4 Sugarcane-Derived Feedstocks

Agricultural by-products are significant resources for biopolymer production due to their high carbohydrate content. Various lignocellulosic residues, including fruit and vegetable waste, are being explored for valorization into bio-based materials. The dual utilization of agricultural residues enhances resource efficiency and aligns with circular economy principles [17].

While carbohydrate-rich crops like corn and sugarcane are pivotal in biopolymer production, oilseed crops such as soybeans provide valuable raw materials for polymer synthesis, offering a different compositional advantage.

2.3.5 Soybean-Based Biopolymers

Soy protein is utilized to produce biodegradable films, coatings, and adhesives [69]. By virtue for their outstanding mechanical features, like emulsification, gelation, foaming, and water and soy protein are appropriate for food packaging applications [69]. Moreover, soybean residues, for instance soybean hulls, have been examined as biopolymer feedstocks, participating in the enhancement of resource efficiency [45].

2.3.6 Other Agro-Based Materials

Starch produced by potatoes and cassava could be hydrolyzed into fermentable sugars, which are suitable to biopolymer production [2]. Additionally, because of their plenty in cellulose and lignocellulosic products like CMC (carboxymethyl cellulose) and cellulose, wheat straw, rice husks, and other cereal by-products show an important part in biopolymer production [52].

2.3.7 Environmental and Economic Impact

To safeguard the long-term practicality of bio-based resources, future investigations must optimize maintainable reserve apportionment. In this line, a strategic shift to second- and third-generation biomass is indispensable to reduce the dependence on first-generation crops [5]. Furthermore, investing in unconventional reprocessing substructure could improve the processing skills, and application of circular economy [48].

2.4 *Biopolymers from Marine and Desert Plants*

For biopolymer fabrication, marine algae and desert plants characterize a highly talented source. Interestingly, their aptitude to propagate in non-arable circumstances rendering them respected.

Marine algae, such as those resulting from seaweeds, could exhibit a great growth rate and use CO₂ efficiently, making them an ecological option for generating biopolymers like polyesters and polysaccharides [70]. Likewise, desert plants, like the prickly pear cactus, presented an extraordinary flexibility to arid climates, demanding negligible water and allowing their farming on marginal lands without competing with food production [71]. Integrating marine and desert biomass into biopolymer production contributes to the sustainability of these resources and aligns with the principles of a circular economy by promoting the use of renewable materials that mitigate plastic pollution and lower carbon emissions [10, 52, 55].

Marine and desert plants have ecological benefits; for instance, algae cultivation for bioplastic production can sequester carbon dioxide from the atmosphere by photosynthesis, facilitating mitigation of global warming and climate change [10, 72]. Replacing fossil fuel-based plastics with algae-based bioplastics reduces greenhouse gas emissions associated with plastic production and disposal, contributing to climate change mitigation efforts [9, 10].

Furthermore, algae-based bioplastics are a viable solution because they can be cultivated in open ponds or photobioreactors, utilizing sunlight, water, and carbon while avoiding direct competition with food crops [10, 72]. This adaptability underscores the potential of marine and desert plants as sustainable feedstocks for biopolymer production.

Polysaccharides like alginate and carrageenan have been extensively exploited for their biodegradable features. These marine-derived polymers display extraordinary biocompatibility and gel-forming abilities, rendering them extremely appropriate for uses in sustainable polymer production [2]. Algae-based biopolymers, in particular, offer a viable alternative, as they can be cultivated in non-arable lands or offshore marine farms, reducing reliance on traditional agricultural resources [10]. Their ability to thrive in diverse environmental conditions and utilize CO₂ effectively makes them a sustainable source for biopolymer synthesis, addressing environmental and economic concerns [71, 72]. Integrating renewable biomass sources, such as agro-food waste, into the biopolymer industry supports circular bioeconomy models by reducing dependence on fossil-based plastics and mitigating plastic pollution. This transition aligns with resource efficiency and waste valorization principles, as agricultural residues can be repurposed to produce biodegradable biopolymers like PHA and PLA. Such advancements reduce greenhouse gas emissions and promote sustainability in material cycles [19, 40].

Among these unconventional feedstocks, marine plants provide an abundant yet underutilized source of biodegradable polysaccharides with exceptional film-forming and moisture-barrier properties, making them particularly suitable for biodegradable coatings, packaging materials, and biomedical applications.

2.4.1 Marine Plants as Biopolymer Sources

Marine plants, including seaweed, macroalgae, and seagrasses, have emerged as promising feedstocks for biopolymer production due to their high polysaccharide content, rapid growth rates, and non-reliance on freshwater or arable land [10, 16]. Polysaccharides included alginate, carrageenan, and agar have excellent and practical characteristics with industrial applications. Alginate is esteemed for its gelation aptitude, elasticity, and robustness. These features were proper to establish biodegradable food packaging and pharmaceutical coatings [10]. Carrageenan is extensively documented for its gelling, and gelling properties, making it a needed element in biodegradable food coatings [2]. Precisely, κ -carrageenan has established their aptitude to prolong the shelf-life of cheese by minimalizing weight loss, refining texture, and highlighting their significance in food packaging [73]. By owing of its structural

integrity and skillful gelation properties, agar was employed in hydrogel formation [74, 75]. Furthermore, agar-based films covered with nanocellulose enhance the mechanical properties, counting tensile strength, elongation at break, and thermal firmness, increasing their utilization in food packaging [10].

Moreover, macroalgae-derived biopolymers reveal characteristic antimicrobial properties, which aid to their potential to prolong the shelf life of perishable food products and improve the food safety [76].

2.4.2 Chitosan: A Key Marine-Derived Biopolymer

Chitosan, a cationic polysaccharide gained from the deacetylation of chitin, is a structural biopolymer originates from the exoskeletons of crustaceans like crabs and shrimp. This cationic nature is recognized to positively charged amino groups, distinctive it from seaweed-based polysaccharides [77]. The deacetylation process eliminates acetyl groups ($-\text{COCH}_3$) from chitin, aggregate its solubility in diluted acids and keep its biopolymeric structure. These features could contribute to outstanding material for numerous industrial applications [33]. In food conservation and active packaging, chitosan was easily employed by virtue of its biocompatibility, biodegradability, and antimicrobial activity [78]. Three-step chemical process—demineralization, deproteinization, and deacetylation—yielded high-purity chitosan with enhanced structural and functional properties [33]. These include a high degree of deacetylation (95.88%), which increases its solubility and bioactivity, and strong water- and fat-binding capacities, which improve barrier functionality in biodegradable coatings [33].

The film-forming ability of chitosan enables its application in active food coatings, significantly extending shelf life by reducing moisture loss, respiration rates, and microbial contamination. Studies indicate that chitosan-coated vegetables stored at $30 \pm 2^\circ\text{C}$ exhibited a 40–50% increase in shelf life. Specifically, chitosan coating extended the freshness of cucumbers, tomatoes, and green tomatoes by up to 21 days, surpassing uncoated controls by 6–7 days, while carrots and beans maintained quality for an additional 12–14 days [33].

The semi-permeable nature of chitosan films creates a protective barrier that modulates gas exchange, thereby inhibiting microbial growth and oxidative deterioration. Statistical analysis validated through FTIR analysis confirmed these findings ($p \leq 0.05$) [33].

Beyond food preservation, chitosan-based membranes have demonstrated promising applications in water purification, biomedical engineering, and pharmaceutical drug delivery systems due to their antimicrobial, hemostatic, and bioactive properties. For water purification, investigation designates that chitosan membranes are widely used in membrane filtration, particularly for removing heavy metals, organic pollutants, and pathogens [32]. Additionally, chitosan-based hydrogels and nanocomposites have shown hemostatic efficiency and antimicrobial capabilities in wound healing and tissue engineering applications [40]. Chitosan-based membranes have demonstrated significant potential in pharmaceutical drug delivery due to their

biocompatibility, biodegradability, and ability to regulate drug release mechanisms. Studies indicate that chitosan is widely utilized as a carrier for controlled drug release, allowing for the gradual and targeted release of pharmaceutical compounds [9]. Additionally, chitosan microneedle arrays have been successfully engineered for the encapsulation and controlled release of active pharmaceutical molecules, such as vascular endothelial growth factor (VEGF), which has applications in wound healing and regenerative medicine [16].

2.4.3 Desert Plants as Biopolymer Sources

Desert plants, uniquely adapted to water-scarce environments, emerge as valuable feedstocks for biopolymer production. Their ability to synthesize polysaccharides with high water retention and structural resilience makes them suitable for biodegradable films, food packaging, and bio-composites. Unlike conventional crops, desert plants thrive on marginal lands with minimal agricultural inputs, reducing competition with food crops while enhancing supply chain sustainability.

Opuntia species, particularly *Opuntia ficus-indica*, have been recognized for their exceptional resilience in arid environments due to their crassulacean acid metabolism (CAM), which enhances water-use efficiency by minimizing daytime water loss [37, 79]. Their ability to thrive on non-arable and degraded land positions them as a highly sustainable feedstock for biopolymer production [80]. By leveraging these attributes, *Opuntia*-based biopolymers contribute to environmentally friendly solutions, reducing the ecological impact of conventional plastic production.

Among the most commercially relevant desert-derived biopolymers, mucilage from *Opuntia ficus-indica* (prickly pear cactus), cellulose and lignin from *Agave* species, and salt-tolerant polysaccharides from *Salicornia* spp. exhibit diverse functional properties. *Opuntia* mucilage, a natural hydrocolloid, has demonstrated high water-binding capacity, reducing moisture loss by over 40% and improving the firmness of coated fruits [80, 81]. It also exhibits bio-adhesive and emulsifying properties, forming stable emulsions and gels suitable for edible coatings and biodegradable packaging.

Recent studies have optimized pectin extraction from *Opuntia* peels, achieving a 19.2% yield using ultrasonic-microwave-assisted extraction. The resulting pectin-based films demonstrated 94% biodegradability and notable antioxidant properties, as indicated by an IC₅₀ value of 232.8 $\mu\text{g/mL}$, meaning that at this concentration, the film exhibits 50% inhibition of free radicals, highlighting its potential as an active packaging material that helps preserve food quality [47]. These properties position desert-derived polysaccharides as high-performance, sustainable alternatives to conventional petroleum-based plastics.

Agave-derived cellulose and lignin significantly enhance the mechanical properties of bio-based packaging materials and composites. Sisal fiber (*Agave sisalana*), a primary lignocellulosic fiber, exhibits a tensile strength ranging from 600 to 700 MPa and a modulus of 38 GPa, making it a viable alternative to glass fibers for reinforcement [34]. Its high crystallinity and lignin content contribute to improved

durability, structural integrity, and environmental resistance, ensuring its suitability for biodegradable composites and sustainable packaging applications. Additionally, its natural resistance to insects and microbial degradation enhances its long-term stability in bio-based materials [34]. Salt-tolerant polysaccharides with hydrocolloid properties enhance biodegradable films' mechanical strength, flexibility, and moisture resistance, making them highly suitable for food packaging and biomedical applications. According to Satchanska et al. (2024), polysaccharides exhibit excellent film-forming capabilities due to their ability to form intermolecular hydrogen bonds, contributing to improved structural integrity and mechanical properties [16]. Additionally, [9] reports that these polysaccharides provide effective barrier properties against oxygen and moisture, thereby extending the shelf life of food packaging applications [9]. Moreover, polysaccharides derived from sustainable and biodegradable resources play a significant role in edible coatings, active packaging, and biomedical films, supporting their use in environmentally friendly applications [82].

Recent studies emphasize the potential of agricultural residues, particularly from food and beverage processing, in developing sustainable biomaterials. For instance, [49] demonstrated how agricultural and food waste derivatives such as bagasse, starch, and chitosan could be repurposed into functional biocomposite materials to produce biodegradable face masks. *Opuntia*-based biopolymer films prove robust O₂ and barrier properties. Sánchez-Vega et al. [81] demonstrated that films from *Opuntia* mucilage exhibit compact, regular surfaces with great water–vapor barrier properties.

On the other hand, desert plants present substitute biopolymers with excellent water retention, biocompatibility and physical stability. These sources are rich on polysaccharides which are proper to establish food packaging.

Beyond their ecological advantages, marine and desert plants contribute to regional economies by creating value-added products from underutilized or waste biomass. For example, the valorization of crustacean shell waste into chitosan provides an industrial pathway for reducing seafood processing waste, while agro-industrial residues from Agave processing are being transformed into bioplastics and composites [49]. Expanding biopolymer markets also present opportunities for economic diversification, particularly in coastal and arid regions, where marine and desert plant industries can foster bioeconomy growth and support rural livelihoods.

Despite the sustainability advantages of recycled polymers in additive manufacturing, several challenges hinder their commercial viability. High processing costs, supply chain constraints, and limited large-scale production capabilities remain significant barriers to widespread adoption. Additionally, the variability in material quality and recycling inefficiencies present further obstacles to achieving consistent performance in industrial applications [48].

Despite their significant environmental benefits, marine, and desert plant-based biopolymers face key barriers to commercial viability. High processing costs limit large-scale production, particularly for algae-derived biopolymers, which rely on costly extraction methods currently constrained to laboratory-scale applications [10, 52]. Additionally, supply chain constraints hinder market expansion and adoption, including a lack of standardization and logistical challenges [18]. Addressing these

economic and technological challenges is essential for the broader commercial success of biopolymers as sustainable alternatives to fossil-based plastics.

Scaling up production will necessitate enzymatic and chemical processing advancements and strategic partnerships between industries, research institutions, and policymakers to support technology transfer and market integration.

Future research should focus on optimizing biopolymer extraction techniques, improving material performance through structural modifications, and expanding industrial applications to meet growing commercial demand. By addressing these challenges, marine and desert plant-derived biopolymers can transform into sustainable materials, reduce reliance on petroleum-based plastics, and advance global environmental and economic sustainability goals.

2.5 *Insect-Derived Polymers*

2.5.1 Overview and Significance

Influenced by the increase of consumer request for maintainable protein sources, the worldwide edible insect market is predictable to reach USD 9.6 billion by 2030 [15]. Insects are examined as ecological replacements to conventional plastics. In this sense, polymers resulting from insects proposed many environmental and economic benefits. For instance, chitin and chitosan, natural polysaccharides, are the most distinguished biopolymers isolated from insect exoskeletons [15, 83].

Insect-based biopolymers own eco-friendly features such as biodegradability and antimicrobial properties [83, 84]. For instance, *Hermetia illucens* is one of the effective insects converting organic waste into valuable biomass by decreasing waste contamination [15, 83]. Recent research directed numerous benefits that insects can deliver. For instance, films produced by chitosan-based insects possessed antibacterial advantages and excellent mechanical barriers [15].

Insect-derived chitosan delivers biodegradability, biocompatibility, and mechanical strength, which could achieve talented unconventional to synthetic plastics in packaging and coatings applications. Chitosan, from *Tenebrio molitor* and *Bombyx mori* exoskeletons, could improve solubility, monitor degradation, and resilient mechanical properties. Additionally, organic waste from *Tenebrio molitor* can be renewed into high-quality chitosan with better antibacterial and mechanical properties.

2.5.2 Green Extraction and Functionalization Techniques

Insect-derived polymers, particularly chitin and chitosan, have emerged as sustainable alternatives to conventional petroleum-based plastics. Their extraction and functionalization are critical to unlocking their full potential in food packaging, biomedical engineering, and agriculture applications. This section explores advanced green

extraction methods and functionalization strategies that align with the principles of the circular economy, emphasizing sustainability, efficiency, and scalability.

Insect-derived polymers, particularly chitin and chitosan, have gained significant attention due to their biocompatibility, biodegradability, and functional properties. Advanced extraction and functionalization techniques are crucial for optimizing their recovery and enhancing their applicability in various fields, including food packaging [15, 83]. Weng et al. [15] highlights the ecological benefits of using insect-derived chitin for packaging films, which exhibit natural antibacterial properties and impressive mechanical traits [15].

Ionic liquids (ILs) are liquid salts composed of organic cations and inorganic or organic anions, which have shown promise in extracting chitin and chitosan. These solvents effectively dissolve and solvate biomolecules, allowing for the liberation of chitin with the simultaneous removal of the protein-mineral matrix [83, 84]. Mei et al. [84] emphasizes that ILs reduce the need for prior isolation and purification of chitin, minimizing chemical usage and process waste [84]. Additionally, ILs can be adapted to optimize interactions with target molecules, enhancing extraction efficiency [84].

Electrospinning is a versatile technique for creating nanofibers from chitin and chitosan, which have broad applications in food packaging and biomedical engineering. This method involves the application of an electric field to draw polymer solutions into ultrafine fibers, which can be functionalized with antimicrobial agents for active food packaging [15, 85]. Insect-derived chitin and chitosan materials are advantageous compared to those from marine crustaceans. For instance, chitosan extracted from sources like cicada slough, silkworm pupae, mealworms, and grasshoppers exhibited greater water-holding capacity (594–795%) and fat-binding capacity (275–645%) than chitosan from shrimp shells [15]. Khatami et al. [85] discusses the fabrication of chitosan films from insect waste, which exhibit antibacterial properties and are suitable for packaging and tissue engineering applications [85]. The resulting nanofibers offer enhanced mechanical and barrier properties, making them ideal for extending the shelf life of food products [83, 85].

Chitosan extracted from *Hermetia illucens* larvae presents a promising bio-based material for applications in biomedical fields, food packaging, and water treatment. Despite its potential, extraction efficiency remains a challenge due to the complexity of insect biomass processing. Current methods rely on acid demineralization and alkaline deproteinization, but yield limitations persist, necessitating further optimization. Industrial-scale adoption is further constrained by economic feasibility, as the high cost of extraction and purification limits its competitiveness with crustacean-derived chitosan. Advances in processing technology and economic models are needed to enhance commercial viability [33, 45, 86].

2.5.3 Applications in Food Packaging and Preservation

Insect-derived chitin and chitosan have been widely explored for their potential in food packaging, particularly as antimicrobial coatings. Weng et al. [15] highlights the natural antibacterial properties of chitosan films, which can prevent microbial

invasion and extend the shelf life of food products [15]. Rehman et al. [83] also emphasizes the alignment of insect-derived polymers with the circular economy principles, as insects can be reared on organic waste, transforming low-value biomass into high-value materials [83].

2.5.4 Sustainability and Economic Considerations

Adopting green extraction techniques for insect-derived polymers offers significant environmental and economic benefits. Mei et al. [84] discusses the sustainability of deep eutectic solvents (DES) and microwave-assisted extraction as innovative methods for chitin recovery. DES offers an environmentally friendly alternative by reducing reliance on harsh chemicals, while microwave-assisted extraction enhances efficiency, leading to faster and higher chitin yields with lower energy consumption and environmental impact [84]. Furthermore, Rehman et al. [83] projects the global edible insect market to reach USD 9.6 billion by 2030, driven by increasing consumer demand for sustainable food sources and innovative biopolymer solutions [83].

2.6 Microbial Biopolymers

Microbial fermentation offers a scalable and sustainable approach to producing biodegradable polymers, such as PHAs and PLA. Despite their environmental advantages, the production cost of PHB, a prominent PHA, remains significantly higher—approximately 4 to 10 times that of conventional polyethylene. This cost disparity is primarily driven by the high price of raw materials and the complexity of the production process, which includes costly carbon sources and multistep synthesis procedures [4, 23]. One of the primary cost contributors is the price of carbon sources, as glucose and refined sugars account for a substantial portion of the total production expenses.

One of the primary cost contributors in microbial biopolymer production is the price of carbon sources, as glucose and refined sugar constitute a substantial portion of total production expenses. The economic feasibility of PHA and PLA production is significantly influenced by feedstock costs, with purified sugars and edible plant oils being among the most expensive due to their relevance to human nutrition. Consequently, alternative sources, such as industrial by-products, are being explored to mitigate these expenses [7, 23].

2.6.1 Utilizing Renewable Substrates in PHA Production

Replacing traditional carbon sources with renewable and inexpensive substrates, such as agro-industrial residues, has shown promise in reducing overall production costs. Studies indicate that feedstock costs contribute to approximately 40–50% of total

PHA production expenses, making waste-based carbon sources a viable alternative [13]. Utilizing lignocellulosic biomass, food waste, and wastewater by-products as fermentation substrates presents a viable approach to reducing raw material expenses in PHA production. Studies indicate that such waste-based carbon sources can significantly cut production costs while maintaining competitive biopolymer yields, making them an effective alternative to conventional feedstocks [23].

Metabolic engineering and process optimization have also been explored to enhance PHA productivity. Notably, integrating waste valorization strategies into the bioprocessing pipeline has demonstrated cost reduction potential, mainly through lowering fixed unit costs and improving energy efficiency. Long-term analyses suggest significant material and energy cost reductions can be achieved through upscaling and process refinement, making waste-based feedstocks a viable alternative [7]. A striking example is volatile fatty acids derived from the anaerobic digestion of shredded office paper, which has been demonstrated as a viable substrate for PHA production. Research highlights the potential of paper and pulp industry waste to enhance microbial PHA synthesis, making waste-based feedstocks a promising alternative for sustainable biopolymer production [5].

2.6.2 Transformation of Agro-Based Feedstocks into Biopolymers

Biotechnological and chemical processing techniques convert agro-based feedstocks into usable biopolymers. A primary pathway involves microbial fermentation, wherein sugars or other organic substrates derived from crops—such as glucose from corn starch or sucrose from sugarcane—are converted by microorganisms into lactic acid, which serves as the monomer for PLA [67].

In an industrial context, the PLA production process begins with the microbial fermentation of corn or sugarcane-derived sugars to produce lactic acid. This is followed by a chemical conversion step, where lactic acid undergoes dehydration to form lactide. The final step involves ring-opening polymerization (ROP), which enables the synthesis of high-molecular-weight PLA. This two-step fermentation and polymerization pathway efficiently leverages agro feedstocks, yielding a durable, biodegradable polyester suitable for packaging and medical devices [7, 67].

Microbial fermentation enables the sustainable production of biopolymer precursors, including organic acids such as succinic acid and butanediol, which serve as key monomers for polyesters and polyurethanes. Specific bacterial strains metabolize sugars, glycerol, and agricultural residues to produce these compounds, supporting the circular bioeconomy using renewable feedstocks [13, 32, 87].

A key aspect of this transformation is the microbial fermentation of agricultural feedstocks, where bacteria and fungi metabolize simple sugars or glycerol into biopolymer precursors. For example, *Cupriavidus necator* and *Bacillus subtilis* have been extensively studied for their ability to convert lignocellulosic hydrolysates into PHAs [32]. Moreover, metabolic and bioprocess engineering advances, including genetic modifications, have optimized microbial strains for improved biopolymer

synthesis. These advancements have enhanced the ability of microorganisms to efficiently utilize agro-residues, such as lignocellulosic biomass and food by-products, leading to higher polymer yields and sustainable biopolymer production [88].

Beyond sugar- and starch-based raw materials, non-food agricultural by-products such as wheat straw, corn stover, and sugarcane bagasse serve as viable and sustainable alternatives for biopolymer production, reducing competition with food supplies. These lignocellulosic materials undergo pretreatment processes, including enzymatic hydrolysis and steam explosion, to release fermentable sugars, which are subsequently used by microbes to synthesize PHAs [87]. Green chemistry approaches, such as enzymatic hydrolysis and supercritical CO₂ extraction, play a crucial role in enhancing the sustainability of agro-based biopolymer production. These methods reduce chemical waste, lower energy consumption, and improve biomass conversion efficiency, offering environmentally friendly alternatives to traditional extraction techniques [87, 89].

The transformation of agro-based feedstocks into biopolymers is a crucial advancement in sustainable material production, providing an alternative to petroleum-derived plastics. This process integrates microbial fermentation and chemical processing to convert renewable resources such as starch, lignocellulosic biomass, and agro-industrial residues into biodegradable polymers like PLA and PHAs. Biopolymers are sustainable alternatives for packaging, medical applications, and biodegradable plastics due to their biodegradability, biocompatibility, and reduced reliance on fossil-based materials. Their wide-ranging applications include regenerative medicine, drug delivery, food packaging, and environmentally friendly bioplastics, making them a key component in the transition toward a circular bioeconomy [9, 40].

Biopolymers represent a critical advancement in sustainable material science, offering significant advantages over conventional petroleum-based plastics. Their development is closely tied to broader sustainability goals, including carbon footprint reduction, waste valorization, and alignment with global frameworks such as the SDGs. As discussed in Sects. 13.1.1 and 13.1.2, biopolymers' life cycle assessment (LCA) consistently demonstrates lower greenhouse gas emissions and improved environmental performance across multiple indicators. However, as highlighted in Sect. 13.2.6.1, their economic viability remains closely linked to feedstock cost, production efficiency, and scalability. Advancing biopolymer technologies will require integrated strategies addressing ecological impact and economic feasibility through policy support, technological innovation, and sustainable feedstock utilization.

2.6.3 Environmental and Economic Impact

The strategic use of agro-industrial residues in biopolymer production aligns with circular bioeconomy principles, significantly reducing costs and environmental impact. Using agricultural waste as feedstock minimizes reliance on fossil-based plastics and addresses agro-waste disposal challenges. LCA studies confirm that

biopolymers such as PLA and PHA substantially lower greenhouse gas emissions and fossil resource depletion than conventional petrochemical plastics [52].

Cost competitiveness remains a key challenge in scaling up biopolymer production due to higher fixed costs and energy-intensive processes. While petrochemical-based plastics remain cheaper due to well-established industrial infrastructure, advancements in fermentation efficiency, feedstock availability, and process optimization steadily reduce production costs. Upscaling and technological learning effects will further narrow this gap [7].

Emerging biorefinery models, where multiple high-value products are derived from a single feedstock, have improved the economic sustainability of biopolymer production by minimizing waste and optimizing resource use [17]. Additionally, the valorization of food waste, such as citrus peels and spent coffee grounds, has been explored as a cost-effective approach for developing biodegradable plastics with enhanced mechanical strength and flexibility, making them suitable for packaging applications [54].

Moreover, consumer awareness and regulatory support are key drivers in the market adoption of bio-based materials. The growing public concern over environmental issues and industry efforts to replace fossil fuel-derived plastics have encouraged governments to implement policies promoting biodegradable alternatives. These policies include restrictions on single-use plastics and incentives to support bio-based material manufacturers [15]. Investments in research and development and industry collaborations are crucial in advancing the adoption of agro-based biopolymers. By integrating sustainability principles and leveraging resource nexus strategies, researchers and manufacturers are developing bio-based materials that enhance cost efficiency and expand application potential in packaging and other industries [19].

2.6.4 Challenges and Future Directions

Despite advancements in agro-based biopolymer production, several challenges persist, including scalability, high production costs, and consumer acceptance. The industrial scalability of microbial fermentation is constrained by economic barriers, including the high cost of raw materials, fermentation media, and downstream processing steps such as extraction and purification [32]. To overcome existing challenges in agro-based biopolymer production, continuous investment is required to optimize microbial strains through genetic engineering, improve bioreactor efficiency via process advancements, and integrate AI-driven process control for enhanced yield and economic feasibility [32, 65].

A significant challenge in the biopolymer industry is the absence of standardized regulatory frameworks to ensure consistency in production, biodegradability, and application. While some governments have introduced policies supporting biodegradable plastics, the lack of globally recognized standards for compostability and certification leads to inconsistencies, affecting market adoption and consumer trust [19, 65]. Future policy developments should focus on harmonizing biopolymer

standards globally while promoting bio-based material adoption in key industries such as food packaging, automotive, and medical sectors. Government intervention through regulations, incentives, and sustainability policies will accelerate this transition [19, 40, 65].

Continued research into bio-based polymer blends and nanocomposites is advancing agro-derived bioplastics' mechanical strength and barrier properties. By incorporating materials such as PLA-PBAT blends and nanocellulose-reinforced composites, these bioplastics are becoming more competitive with traditional petroleum-based materials, particularly in packaging applications [9, 10, 19]. Integrating bio-nanofillers, such as cellulose nanocrystals and chitosan nanoparticles, significantly enhances the functional properties of biopolymers. These enhancements include improved mechanical strength, thermal stability, and controlled-release capabilities, making them more suitable for high-performance applications in packaging, biomedical materials, and smart-controlled release systems [9, 10, 16, 26].

3 Advances in Biopolymer Manufacturing Technology and Sources for Environmental Sustainability

The expansion in the production of both biopolymers and synthetic ones is attributed to advances in current manufacturing technologies to meet the growing needs of consumers. Recently, because of the diversity of biopolymers, different advanced production techniques are demanding. Innovations utilize cutting-edge technologies, new raw materials, and integrated processing approaches.

In the next section, we explore key strategies for producing biopolymers in the food industry, which rely on environmentally friendly solutions.

3.1 Waste Food as a Production Material Source for Biopolymers

Food waste is one of the key issues of modern life. According to the Food and Agriculture Organization (FAO) estimates, global food waste exceeds 1 billion tons annually [90]; they are considered a potential biopolymer production feedstock. Food waste is rich in biodegradable organic components composing proteins, carbohydrates (such as starch and cellulose), fibers, and other essential nutrients. Thus, the moist composition creates an ideal environment for microbial growth [91]. The variety of compositions of waste food can be used for polymer-based composites [92]. This food waste includes dairy, agricultural, fruits, vegetables, cooking oil, meat, seafood, and grain and animal-based waste. Using food waste for biopolymer production is an available, eco-friendly, and cost-effective process for environmental sustainability.

An example is the making of bioplastics from waste food, which has shown dramatically reduced carbon footprint emissions and non-renewable energy consumption compared to traditional plastic manufacturing from petrochemical sources [93].

3.2 Biopolymer Production from Waste Food Approaches

The production of biopolymers from food waste involves sorting the food waste, coupling it with chemical extraction, and then subjecting it to microbial-assisted production, enzymatic, or heat application for mediated production. Microbes' application in synthesizing biopolymers is a powerful tool, as it is easy to manipulate and upscale.

Microbial biopolymer production is the most common method used in biopolymer processing. However, the utilization of microbes in biopolymer production has been subjected to development using various technologies, as will be discussed in the following subsections, with a focus on the technologies applied mainly in food packaging industries since it is the most dominant area in biopolymer application within the food industry.

3.2.1 Innovative Processes in Biopolymers Production

Genetic Engineering

Due to genetic engineering and synthetic biology advancements, microorganisms have enhanced the efficiency of producing diverse biopolymers for various applications. As a result, offering sustainable alternatives reduces reliance on petrochemical resources and decreases environmental impact.

Genetic engineering is one of the most innovative technologies for biopolymer production. It involves engineered microorganisms (i.e., *Escherichia coli* and *saccharomyces cerevisiae*) that can produce desired biopolymers, improve their properties, and increase the production scale, including bioplastics. This involves several common biomaterials, such as PHAs [40], starch, cellulose, and alginate [94]. Genetic modifications involve manipulating metabolic pathways, altering enzyme-encoding gene expression, and enhancing substrate uptake, which improves biopolymer production. The advancement in OMICs technologies unlocks the potential of genetically and metabolizing microorganisms to improve the characteristics of biopolymers and upscale their production [95]. Further advanced technologies such as CRISPR-Cas9 permit precision editing of the genome [96]. The following are some examples of biopolymers that were subjected to the genetic modifications process to enhance production and characteristics:

- **Starch** is a natural polymer that can be obtained from plants such as cereals, legumes, and other plant residues. It is abundant even in food waste and cost-efficient; therefore, it has been used to produce biodegradable films [97]. Cassava starch has gained a high interest in the last decades as a source for developing food biofilms. Various modifications were applied to starch to improve its mechanical and isolating properties [98].
- **PHAs** can be produced by the genetic modification bacteria. A study reported that overexpressing specific proteins in *Synechocystis cyanobacteria* under nitrogen-limited conditions increased PHA yields by 2.6 times, enhancing industrial viability [99].
- **Cellulose** is a natural biomaterial from plants. Engineered bacteria can also produce cellulose [100]. Bacterial cellulose (BC) possesses a special character. It is a nanofiber biomaterial produced by single cells. In recent years, materials have been designed using engineered bacteria to produce cellulose with specific characteristics and various applications, including food packaging. Synthetic biology strategies have been developed to improve the microbial synthesis of cellulose, making it a more sustainable and customizable material for various applications [101].
- **Alginate**, a polysaccharide obtained from brown algae, is used intensively in food and biomedicine. It has a favorable property [102]. Genetic modification approaches have been employed to enhance microbial production of alginate [103], offering a more sustainable and controlled production method than traditional extraction from brown algae. Alginate has been improved to increase its stability under various thermal conditions, which adds further desirable features for application in the food industry [104]. For instance, engineered alginate extends the shelf life of food products as it maintains moist and oxygen levels [105].

Three-Dimensional (3D) Printing

Recently, significant attention has been given to using 3D printing technology with bio-based polymers due to its potential to create sustainable materials [106]. Bio-based polymers, derived from environmentally friendly resources (i.e., plants, microorganisms, and algae) [107–109], create a promising alternative to petroleum-based plastics. Materials such as PLA are sourced from renewable biomass and are compostable, which decreases environmental plastic waste [110]. Utilizing 3D printing enables the production of structures at high speed and with minimal waste, which can support the development of specialized and unique products. This approach can be valuable in medical device manufacturing and custom consumer goods [111]. While 3D printing uses additive processes that only depend on materials required for the final product, traditional synthetic manufacturing processes (e.g., injection molding) waste material by consuming excess amounts [112].

3D printing relies on several approaches. First, fused deposition modeling (FDM) is commonly used in 3D printing and works well with bio-based filaments like PLA. The final product is formed by depositing layers of polymer extruded via a heated nozzle [113]. The second technique is called Stereolithography (SLA), where liquid resins—depositing layer by layer—cure into solid structures using ultraviolet (UV) light. Recent advances have concentrated on bio-based resins from renewable feedstocks, which may be utilized in medical devices and other specialized goods [114]. Third, selective laser sintering (SLS) uses a laser to sinter powdered material, layer by layer. Research into bio-based powders, such as those derived from PLA or PHA, has shown that SLS can effectively print bio-based polymers with better mechanical properties [115]. Finally, Inkjet printing and direct ink writing (DIW) allow for the deposition of bio-based inks or pastes, including hydrogel-based or polymer-based inks, to create 3D structures. These techniques are beneficial for printing complex, high-performance materials like tissue scaffolds [116].

3D printing methods are compatible with several biopolymer types. Here are some of the most common bio-polymers:

1. PLA

Consider as one of the most used bio-based polymers in 3D printing because it is easy to print and can tolerate a wide range of temperatures [117]. These bio-polymers originated from diverse sources like plants (e.g., corn starch and sugarcane) [118]. It is a novel biodegradable polymer under industrial composting conditions [119]. PLA is widely used in FDM, an innovative processing technology for thermoplastic and environmentally friendly materials [120]. Due to its ease of processing and low toxicity, it has become a suitable process for various applications, from prototyping to consumer products [110, 114].

2. PHAs

PHAs are biodegradable thermoplastics produced from waste food by microorganisms during fermentation [121]. PHAs are attractive for 3D printing due to their biodegradability and biocompatibility, though they have been less commonly used than PLA in commercial 3D printing. However, research is developing combinations between PHA and PLA with various printing densities to examine durability and environmental degradation, especially in marine ecosystems [122]. Further ongoing research is focused on improving their mechanical properties for broader applications in 3D printing [123, 124]. However, the materials' high cost and the media's cultivation limit upscale production [121].

3. Polybutylene Succinate (PBS)

PBS is another bio-based polymer with biodegradability properties suitable for 3D printing. PBS is an environmentally safe biopolymer with attractive properties like good clarity and processability, shiny appearance, and flexibility; PBS will degrade in the soil much quicker than similar petrochemical plastic [125]. It is produced from renewable resources and offers good mechanical properties, though its use in 3D printing is still in development [126].

4. Chitosan and Chitin

Derived from the exoskeletons of crustaceans, chitosan and chitin have 3D printing applications because of their highly stretchable, ultrathin, lightweight, and flexible features [127]. These polymers are biodegradable and biocompatible, making them ideal for printing scaffolds for tissue engineering and other biomedical applications [128, 129].

Nanotechnology

In the last era, nanotechnology has gotten notable attention in different industries, mainly biopolymers. Integrating nanotechnology in biopolymer production enhances the properties of biopolymers, providing improved performance, sustainability, and functionality as an eco-friendly alternative to petrochemical polymers. However, their mechanical properties and performance often fall short compared to synthetic polymers. The novelty of this technology addresses these limitations by incorporating nanoparticles into biopolymers. The innovation or novelty of this nanotechnology can overcome the current limitations by incorporating nanoparticles into the biopolymer structure. Thus, their properties are enhanced by improving biopolymer structure, boosting thermal stability, increasing mechanical strength barrier properties, and adding functions like antimicrobial, antioxidant, and drug delivery capabilities.

Nanoparticles like nanocellulose (NC), nano-silica (NS), and nano-clay (NCI) are commonly used to enhance biopolymers' physical properties [130–133]. Incorporating nanoparticles into biopolymers' construction can significantly improve their tensile strength and make them impact resistant. For instance, nanocellulose, derived from plant fibers, has improved biopolymer matrices' mechanical properties and stability [134]. In addition, involving nanocellulose in biopolymer composites can enhance their sustainability by boosting their biodegradability and thermal stability, making them more viable for industrial applications such as packaging and medical devices, according to studies [135].

Furthermore, this technology enables biopolymer functionalization, introducing nanostructured surfaces or adding nanoparticles that can impart new properties to biopolymers (e.g., self-healing, antimicrobial, and chemical-release capabilities [136]. For instance, antimicrobial properties can be formed by incorporating silver nanoparticles (AgNPs) into biopolymer matrices, thus becoming suitable for food packaging and medical device applications [137]. Likewise, nanostructured biopolymers are being developed for controlled and targeted drug delivery systems, offering an innovative solution to food and medical treatment delivery [138]. Combining nanotechnology with biopolymer manufacture also produces more sustainable products. For instance, including nanoparticles makes the products biodegradable and offers better performance simultaneously [139].

4 Applications in the Food Industry

The food industry has faced criticism for its reliance on non-biodegradable, environmentally harmful, and toxic production methods, materials, and treatment practices. Traditional plastics, derived from non-renewable petroleum resources, pose significant environmental and sustainability challenges. Food-grade plastics, such as polyethylene terephthalate, polypropylene, and high- and low-density polyethylene, are FDA-approved for food contact and are widely used due to their ease of manufacturing, performance, customizable properties, and convenient disposal [140]. Despite their versatility, these materials are non-biodegradable, leading to their buildup in ecosystems and causing significant ecological and health problems. For this reason, the concept of a circular economy is gaining attention, focusing on creating biodegradable or recyclable materials to cut waste and reduce the carbon footprint of packaging industries [55]. This opens the door for edible and biodegradable biopolymers in food production and packaging. They are suitable for use as coatings, films, packaging, and protective or preservative materials, offering eco-friendly solutions to traditional plastic use.

Currently, the main drawback of biopolymers is their high cost, which ranges from approximately 4,000 to 15,000 USD per metric ton, in stark contrast to synthetic polymers, which cost around 1,500 USD per metric ton [141]. However, the cost of biopolymers is anticipated to decrease as more manufacturers in Europe, the USA, China, Japan, Thailand, and India adopt biopolymers and integrate advanced manufacturing technologies [142].

4.1 Food Products

4.1.1 Edible Films and Coatings for Food Preservation and Extended Shelf Life

Edible films and coatings are thin layers, typically less than 0.3 mm thick, made from edible materials that can be directly consumed [143]. The key distinction between these food systems depends on their application: edible coatings (EC) are used on the food in liquid form, typically by dipping, spraying, or brushing the product with a solution made from structural matrix-based biopolymers like carbohydrates, proteins, and lipids. In contrast, edible films (EF) are formed into solid sheets through casting or extrusion, which are then used to wrap or cover the food product [144]. Both systems target the creation of protective barriers that help to extend shelf life, decrease moisture loss, and enhance the appearance of the food product [145].

The food industry has shown growing interest in edible films and coatings. A PubMed search using the keywords “edible coatings and film in food” yielded 1,126 publications between 1995 and 2025. The search, confined to the last two decades using PubMed, reveals that the number of publications in this area has increased

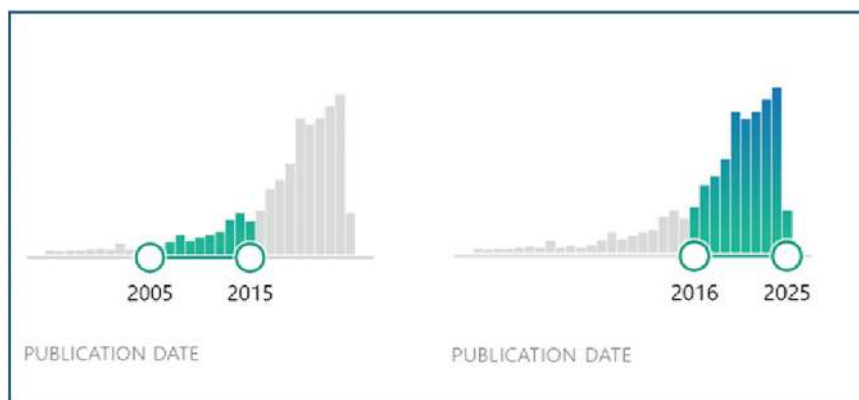


Fig. 13.1 Evolution of the number of publications about edible coatings and films in foods between the last decades. The result was obtained from PubMed. (<https://pubmed.ncbi.nlm.nih.gov/?term=edible+coatings+and+films+food>). Furthermore, accessed on 1 March 2025

more than fivefold compared to the previous decade, as illustrated in Fig. 13.1. Notably, publications from 2020 to 2025 alone account for nearly 75% of all literature published in the last ten years.

As an alternative, these biopolymers can be utilized entirely in the food chain by being extracted from agro-industrial waste as sources of valuable materials for manufacturing films and coatings [146]. These biopolymeric systems have been shown to have distinct benefits, including being nontoxic, biodegradable, and acting as a barrier between food and its external environment. They typically enhance food quality by inhibiting microbial growth through the intrinsic antimicrobial properties of substances like chitosan and plant extracts and by preventing oxidation, such as using green tea extract to maintain the freshness of sausages [147–149]. Edible films and coatings can also ameliorate the shelf life of food products and their nutritional content [150].

4.1.2 Functional Materials for Eco-Friendly Food Processing and Storage Solutions

Over the past ten years, food packaging scientists have become increasingly concerned about creating municipal solid waste based on plastic [151]. Using natural polymers as possible food packaging materials has recently been the subject of extensive research. Many classes of biopolymers, including gelatin, collagen, and polysaccharides (chitosan, cellulose, pectin, starch), have been used extensively to create packaging films and coatings for food products. Active food packaging incorporates functional materials directly into the packaging that can interact with food to preserve quality, prevent spoilage, and extend shelf life [152]. In this context, introducing eco-friendly materials plays an important role in the current global changeover

model to a circular economy and the potential for giving these materials active functionalities that reduce food additives [153]. For example, including antimicrobial and antioxidant agents in active packaging materials can help efficiently safeguard food from spoilage factors. In this regard, metal oxide nanoparticles are the most often used materials for boosting food packaging biopolymers' physicochemical characteristics and functioning [154]. According to Bajer [151], starch-based films reinforced with dialdehyde starch and supplemented with antioxidants, such as lipids or vitamins (tocopherols, carotenes, carotenoids, and ascorbic acid), are substitutes for packaging applications where oxidation protection is necessary [151].

4.2 Food Packaging

4.2.1 Biodegradable and Compostable Packaging to Replace Single-Use Plastics

Food packaging accounts for roughly 5.4% of global greenhouse gas emissions [155]. The global population, projected to reach approximately 10.3–10.5 billion by 2050, coupled with rising food demand, has significantly boosted the production of single-use plastic packaging systems [155, 156]. This amounts to 23 million tons in Europe alone, with estimates suggesting a surge to 92 million tons by 2050 [157]. These packaging systems have an extremely short life cycle, rapidly turning into waste that requires disposal. Single-use plastics pose a significant threat to the environment, and they deplete essential resources. Additionally, they degrade natural landscapes, source harmful chemicals, and penetrate the food chain through microplastics [158].

Biodegradable polymers have been considered a promising alternative to non-degradable plastics due to the pressing need to address the environmental issues posed by plastic waste at the end of its life cycle. Countries worldwide are enacting regulations to promote the necessity of replacing traditional non-biodegradable plastics with sustainable alternatives. Although, conventional materials-based cellulose such as paper and cardboard continue to dominate the food packaging industry and sustainable alternatives like starch, PBS, PLA, polybutylene adipate terephthalate (PBAT), and PHA are receiving growing global attention as eco-friendly options [159–161].

4.2.2 Smart Packaging with Antimicrobial Properties and Extended Shelf-Life Benefits

Smart packaging systems such as active and intelligent packaging are based around the beneficial interaction between the packaging environment and the food to offer active protection to the food. These systems enhance food preservation by dynamically responding to changes in the storage environment, ensuring better quality and safety.

Smart packaging technology in food preservation has demonstrated significant promise driven by continuous advancement in science and technology. By incorporating advanced sensors, innovative materials, and Internet of Things (IoT) capabilities, smart packaging allows real-time monitoring and control of storage conditions, thereby improving food safety and shelf life [162]. Food products are perishable, and their quality can vary significantly due to temperature, humidity, and gas composition. Smart packaging technology can help extend their life by monitoring and controlling these environmental factors in real time, which is one of its key benefits. Intelligent packaging has been conveyed using food waste extracts to perceive variations in temperature/time, humidity, pH, CO₂, methylene, other gas production, and microbial development [163].

Additionally, between the primary intelligent packaging, indicators (specifically pH-sensitive intelligence) and sensors (e.g., gas sensors, time–temperature, and humidity) tools are the leading exploited indicators [164]. For example, by integrating temperature and humidity sensors into smart packaging systems, it is possible to continuously monitor the storage conditions of fruits and vegetables during storage and transportation, guaranteeing that they are kept in ideal preservation environments and thereby extending their shelf life [165]. Considering their potential to frankly envisage any fluctuations in the quality of products through transparent packaging, optical sensors were considered a stimulating alternative for application in intelligent food packaging [166]. Furthermore, adding biodegradable materials and active ingredients can significantly reduce microbial contamination during storage, extending food products' freshness and shelf life [167]. Some smart packaging materials possess functional properties, such as antibacterial and antioxidant capabilities, which actively prevent the growth of bacteria and mold. These smart packaging structures have widely developed natural pigments like curcumin, betalains, carotenoids, anthocyanins, and polymer-carriers like starch, gum, and chitosan. Recent studies have explored plant extracts as valuable compounds derived from food processing by-products and food waste to achieve sustainable development goals [168, 169]. For example, waste from date and beetroot, rich in anthocyanins and betalains, was incorporated into a carboxymethyl cellulose-based matrix [170, 171]. The pH-sensitive films developed effectively monitored the freshness of minced beef stored at 4 °C for up to 14 days. The Internet of Things (IoT) is a network of interconnected systems that facilitates digital data exchange between information technology systems, sensors, controllers, and other digital devices. This explains the name “Internet of Things,” referring to its two main components: “Internet” and “Things” [172]. Key benefits of IoT in the food sector include enhanced transparency, improved organization, better traceability, verification of quality attributes, and tracking of consumer data [173]. Furthermore, IoT can strengthen consumer confidence in food product quality and manufacturing processes by providing detailed information on quality or labels.

4.3 Global Case Studies

4.3.1 Examples of Successful Integration of Biopolymers in Food Products and Packaging Worldwide

In 2022, the total amount of bio-based plastics produced worldwide was 2.2 million tons, accounting for less than 1% of all plastics produced worldwide (European Environment Agency, 2024). Numerous environmentally friendly packaging choices were found, including biopolymers like PLA. For instance, PLA is the most representative example of biodegradable packaging obtained from starch by fermentation [174]. As renewable, microbially produced, and compostable polyester, PLA can be treated using methods similar to many conventional commodity plastics [175].

Because PLA is made by polymerizing lactide acid (LA), which can be extracted from various culinary and agricultural waste products, it is considered an inexpensive and sustainable substitute precursor material for creating polymer matrices [176, 177]. It is made from renewable resources like sugarcane or corn starch and has good mechanical, thermal, and biodegradable qualities, which make it a good substitute for traditional plastics made from petroleum [178]. An additional benefit of PLA is its capacity to be utilized in industrial melting-blowing processes to create packaging films [179]. Therefore, PLA may eventually replace fossil-based polymers in the food packaging sector [180, 181].

PLA has emerged as a leading biodegradable biopolymer, especially in the food packaging industry. Although, the drawback of PLA is its limited mechanical and thermomechanical properties. Researchers have enhanced PLA by incorporating bio-based plasticizers to address this limitation [182–184]. Triethyl citrate (TEC) is a newly discovered food-grade, bio-based plasticizer for PLA that shows promising potential. This substance enhances PLA's viscoelastic qualities, and the PLA/TEC new self-healing composite matrix showed better antioxidant and antibacterial activity and improved water/oxygen barrier qualities [184]. Incorporating cellulose nanocomposites can also address these drawbacks [185]. When added to PLA film, cellulose-based nanofibers demonstrated improved material strength and barrier qualities [186]. Additionally, cellulose fibers enhance the thermal performance of PLA [187].

5 Circular Economy and Sustainability Impact

5.1 Circular Bioeconomy Framework and Economic Feasibility

Although the definitions of bioeconomy and bio-based products change by country due to divergent concerns, they have the same important conception: “*expanding the exploitation of biological products and methods through economic sectors for environmental and economic welfare* [188].” For example, the Bio Preferred Program, accredited by the United States Department of Agriculture (USDA), promotes the increased purchase and use of bio-based products in the U.S., aiming to drive economic growth, create new jobs, and open new markets [189]. Techno-economic analysis (TEA) is a well-renowned scientific tool for assessing the sustainability of bio-based products and creating knowledgeable choices [190]. The TEA employed data from material and thermodynamic documents for process improvement and practical optimization that authorizes us to appreciate the financial and technical feasibility of processes, services, or products [191]. TEA permits us to understand the long-term economic influences of skills at different commercialization steps and to classify the hotspots for attaining cost reduction marks [191].

Fabricating bio-based polymers, consequent to sustainable resources, could provide a sustainable, eco-friendly substitute for conventional fossil-based plastics. They contribute to environmental sustainability by reducing greenhouse gas emissions and dependence on nonrenewable reserves. By 2026, the worldwide market for green polymers, comprising bioplastic packaging materials, is estimated to attain US\$ 30.0 billion [192]. However, the high cost of biopolymer production remains a significant challenge, as additional bioprocesses such as fermentation, extraction, and purification can further increase costs, making them more expensive than fossil-based polymers. Additionally, to fulfill industrial scaling-up production, higher convenience costs and the inferior physical–mechanical features of biopolymers also rest. This latter disadvantage makes biopolymers less suitable for specific industrial applications. Through 2020, it was estimated that biopolymer production volume would attain 2.9 million tons by 2025.

Nevertheless, this amount is inadequate against the market need of 360 million tons [193]. Improving the economic performance of bio-based polymers will depend on early stage innovation in biomass selection and process design, setting the foundation for future advancements addressed in later sections. Notwithstanding these tasks, the bioplastics market is increasing in various areas, including packaging and coating. In 2020, packaging was the leading utilization, illustrating 50% of the total bioplastics market [194]. Regarding market sustainability, bioplastics are well-stated to support the circular economy. Biopolymer production uses agricultural food waste to meet zero-waste standards and ecologically sustainable practices [195]. For instance, the European Union (EU) helps with eco-friendly development and practical biopolymer products across financial and legislation directives by funding biopolymer scaling-up production.

Whereas agricultural wastes are usually employed to produce first-generation biodegradable bio-based polymers, the investigation into second- and third-type polymers has centered on feedstock material that would be practicable for generating these polymer kinds. The second and third-generation biodegradable bio-based polymers are crucial, as they enhance economic viability by prolonging the product life cycle, receiving us closer to a circular economy. Some pioneer materials that produce second-generation biodegradable bio-based polymers comprise non-food crops and by-products from first-generation feedstock, such as wood, sugarcane bagasse, switch grass, corn, and palm [196]. Some illustrations of feedstock material employed for third-generation biodegradable bio-based polymers contain municipal and industrial waste and biomass algae [196].

The market adoption, incorporation, and acceptance of new biopolymer machineries must be meticulously managed [197]. First, there is a demand for plans to inform organizations and customers about the suitable classification and management of bio-based products. This fact was attained by providing a complete assessment of the environmental influences linked to biopolymer production. At all agricultural circular economy steps, LCA is perfectly adapted for assessing the impact of the ecosystem. This system employed unconventional technologies for minimizing waste through a closed-loop system [198]. Toward the effective development of a circular economy, technologies for conserving the balance of economic/industrial development and protecting the ecosystem with the operative use of resources were well involved. To analyze the environmental materials implications, LCA could examine the products during their life cycle at all stages [199] by performing a general view of (i) sustainability, (ii) health/safety impacts, (iii) life cycle estimation, and (iv) social deficits [12]. In addition, LCA is the principal in this progression and can control organizations and customers by creating reasoned solutions, guaranteeing that bio-based products are correctly categorized and encounter sustainability standards throughout their life cycle. In this connection, “greenwashing” is employed to classify products as natural, compostable, or biodegradable [200]. To beat this hurdle, a comprehensible and perfect announcement directed toward consumers who are slightly uncertain and suspicious of approving new biopolymer technologies is necessary [201]. There is a clear need for information movements to instruct participants on the dangers and limits linked to new biopolymer tools [202]. Moreover, attempts should pay attention to cumulative public consciousness of the personal assistance of new biopolymer products [203]. Such campaigning should be recurrently verified with memberships of the proposed audience and their supervised consequences [203]. Consequently, it is pertinent to prolong existing information to comprehend biopolymers’ large-scale applications well and establish recognizable important products that can draw and preserve market attention [204]. Lastly, novelty approaches, stakeholder responsibility, and public engagement are wanted to increase public acceptance (Fig. 13.2).

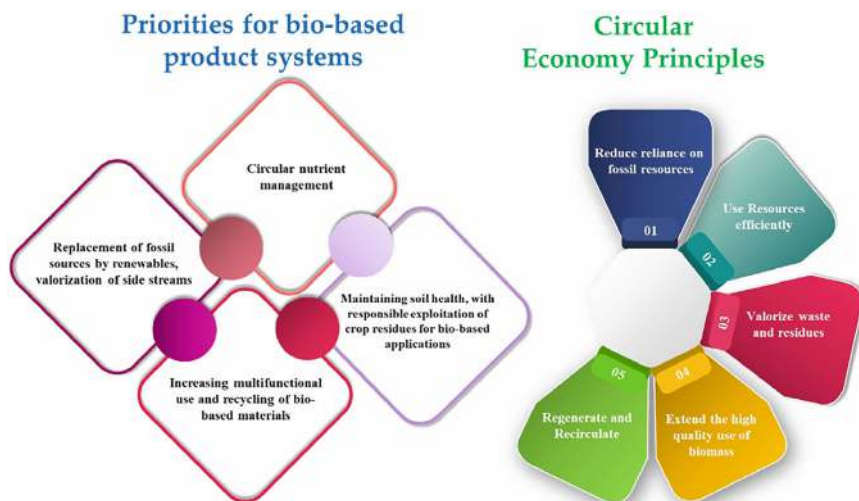


Fig. 13.2 Bio-based product system priorities and the distinct circular economy principles

5.2 Environmental Benefits

Food plastic-based packaging occupies a special interest because of its catastrophic ecological impact and inherent human health hazards. Undeniably, along with their potential liberation from packaged food endangering food safety and quality, synthetic plastic materials are scarcely self-degradable, provoking greenhouse gas (GHG) emissions. Plastic manufacturing prompts significant GHG emissions and consumes the most fossil-based energy in countries in total fossil fuel consumption. As an illustration, in 2018, principal petrochemical production provoked ≈ 880 million tons of direct CO_2 emissions, corresponding to a 4% increase compared to 2017 [205]. LCA investigations on bio-based plastics have exposed that the employment of these materials is valuable in terms of GHG emissions reduction and energy savings [206]. For instance, almost 40–50% convertible of nonrenewable energy was utilized, and a 50% reduction in GHG emissions has been stated in a comparable cradle-to-grave impact study of production between Polyethylene Furanoate (PEF) and Polyethylene-Terephthalate (PET) [207]. It should be noted that the environmental influences of bio-based plastics production are characteristically controlled by the origin of primary materials comprising first-generation agricultural farming [207]. The primary GHG emissions sources are water, energy input in the form of fossil fuel, and fertilizer inputs.

Additionally, the greatest commercial production of bio-based plastics feedstocks necessitates significant arable areas to cultivate, which is also a concern for the environment [207]. Nevertheless, the existing bioplastics production is projected to

convert to ≈ 0.5 million ha of land, corresponding to 0.04% of farmland. If, hypothetically, all the plastics became biomass-based, there could be an issue due to the land required, and the present level of total plastics production would need roughly 25–30 EexaJoule (EJ); $1\text{ EJ} = 10^{18}\text{ J}$ of natural gas feedstocks [208]. Another difficulty with bioplastics is restricted or no organization for their collection [209]. According to [210], several countries preferred incineration for energy. Some investigations on GHG emissions to bio-based products, comprising bioplastics and biofuels, evidenced that overall GHG emissions could be moderated in contrast to petrochemical products by harnessing CO_2 sequestration from the atmosphere through photosynthesis throughout plant growth [211].

The coming time of biopolymer is chiefly tracked by the ecological footprints and guidelines instead of market equities. In future years, the demand for biopolymers will be more severe, influenced by technological growth [207]. In this line, advanced tools deliver the possibility for a biopolymer circular economy; realizing these proposed benefits depends on ensuring the circularity of all materials throughout the stages of research, development, and production. Lately, there has been a debate regarding engendering a bio-based economy to produce bio-based products, including bioenergy/biofuels and chemicals [212]. A bio-based economy might introduce possibilities to local farmers across an expanded agricultural output for food, feed, and industrial needs, consequently providing more stability and security to locals [207]. Throughout the regional feedstock production line for bioenergy and bio-based products, farmers can implement the best precision agriculture, diminish GHG emissions, and improve resource efficiency, which is advantageous for the socioeconomic welfare of agricultural regions [213]. In addition, the biomass flux and strategies allied with the values of the circular economy could be a very productive model to obtain a complete bioeconomy value chain [211]. The principle also guarantees the insertion of new biomaterials with pioneering functionalities that unlock prospects for the progress of new process technologies.

6 Challenges and Future Directions

6.1 Scalability and Industrial Adoption

Nowadays, the demand for biodegradable biopolymers has considerably increased due to consumer awareness of the harmful environmental impacts of contamination of landfills and water resources by single-use petroleum-derived synthetic polymers [214]. Even though there are evident economic challenges in switching to biopolymers because of their exorbitant cost of mass-scale production, they have been shown to play a significant role in enhancing life cycle sustainability and circular economy.

The commercial impact of biopolymers is not limited to the packaging industry; it extends to the medical and biomedical fields, where they are applied in surgical, drug delivery, and medical implants [215].

To overcome the barrier to industry-wide adoption of biodegradable biopolymers like PHB, PBS, and PLA, it is essential to reduce their high cost of production [216–218].

For instance, Price et al. suggested the substitution of organic carbon substrates for fermentation by atmospheric CO₂ to produce PHB by cyanobacteria [219]. Also, bio-based PBS can be made using sugar cane, corn, sugar beet, and potato, which have minimal land and water needs [220].

6.2 Regulatory Alignment

Petroleum-based single-use synthetic polymers are associated with diverse health and environmental concerns throughout their life cycle. These include pollution, emission of greenhouse gases, and persistence of contaminants in aquatic and terrestrial environments. Banning synthetic polymers and replacing them with biodegradable, fast-expanding biopolymers is crucial in decreasing those environmental hazards considerably. Initiatives for implementing regulations to reduce single-use plastics and encourage the production and usage of biodegradable biopolymers will create an auspicious market for bio-based polymers and prompt more sustainability in polymer manufacturing practices [221]. Hence, there is a need to rationally analyze the advantages and disadvantages of using biopolymers and especially evaluate the correct impacts of their adoption on human health and the environment [222].

6.3 Emerging Technologies

AI-powered predictive modeling has proven valuable for designing and producing biomaterials, illustrating their features, and predicting their efficacy. Indeed, using conventional procedures to evaluate biomaterial characteristics like rigidity, biocompatibility, and degradation rate is generally costly and time-consuming. Conversely, AI predictive algorithms can assess these properties for novel biomaterials with known chemical composition by exploiting biomaterial feature data [223]. Moreover, AI can develop computer-generated prototypes and predict *their performance* in silico, speeding up the biopolymer design process. This is particularly advantageous in the food and packaging industries, as AI can also support personalizing and adapting biomaterials to meet the specific requirements of each product [223].

Many companies are currently utilizing AI to develop biomaterials. Among them is Atacama Biomaterials, which utilizes AI to predict the mechanical resistance of materials used in the packaging industry by exploiting the original data stored from those materials and subsequently making predictions of new formulations [224]. In a

previous study, Signori-Iamin et al. [225] applied three machine learning algorithms, namely, multiple linear regression (LR), random forests (RF), and artificial neural networks (ANN) to predict key properties of cellulose that are micro/nanofiber aspect ratio and yield of nanofibrillation. The findings of this study proved that machine learning models showed promising results, especially ANN [225].

Incorporating nanofillers, including nanoparticles (NPs) or nano-clays, into biopolymer matrices has been confirmed as a helpful approach to overcoming intrinsic biopolymer limitations. It can enhance mechanical strength, gas barrier characteristics, and thermal stability. This synergistic strategy has led to nanocomposites exhibiting enhanced performance while retaining the beneficial eco-friendly characteristics of biopolymers, including the absence of cytotoxic product release on degradation [226]. Several fabrication methods can be employed for developing biopolymer nanocomposites, such as solution casting, melt mixing, and extrusion. For instance, different biopolymers, such as starch, cellulose, and proteins, have been utilized to develop nanocomposites for food packaging. Challenges persist regarding these biopolymer nanocomposites for application at the industrial scale. Reaching an equilibrium between enhancing material features and confirming cost-effectiveness remains a substantial barrier to addressing these challenges and the widespread implementation of nanocomposites based on biopolymers in food packaging and tissue engineering.

6.4 Research Opportunities

Insects and microorganisms are considered among the principal sustainable substitutes for conventional plant-derived biopolymers. For instance, chitosan is among the most promising and effective natural polymers because of its outstanding antimicrobial and antifungal properties [227, 228]. It is derived from the alkaline deacetylation of chitin, which is mainly extracted from the exoskeleton of crustaceans. However, chitin is extracted from more sustainable sources, primarily insect larvae, specifically the converter *Hermetia illucens*. In addition to the antifungal activity of chitosan verified on many fruits, this polymer can also prevent fruits from browning, which causes substantial economic losses. The limitation of using chitosan as a film is its poor stability at acid pH. For this reason, it can be functionalized by doping with additional materials to improve the functional characteristics. On the other hand, microorganisms are well known for their capability to synthesize biopolymers, especially polysaccharides, polyamides, and polyesters, which can potentially be biomaterials. Thanks to their exceptional attributes, microbial biopolymers can be applied in several sectors, such as agriculture, food, and textiles [229].

7 Conclusion

This chapter has comprehensively explored recent advancements, and the transformative potential of biopolymers derived from organic waste and agro-based feedstocks, emphasizing their innovative applications in sustainable food products and packaging. Through advanced technological approaches such as microbial fermentation, enzymatic hydrolysis, green chemistry, and nanotechnology, biopolymers have substantially improved mechanical strength, biodegradability, barrier properties, and overall environmental performance. Valorization of diverse feedstocks—including agricultural residues, marine and desert plants, insect-derived polymers, and microbial biosynthesis offers promising solutions to mitigate plastic waste accumulation, reduce greenhouse gas emissions, and support circular economy practices.

Many challenges persist despite these significant innovations. Technical scalability efficiency, cost competitiveness with traditional plastic, stable feedstock supply, efficient processing technologies, and regulatory constraints pose substantial barriers to widespread industrial adoption. Addressing these problems involves focused research and development, technical innovation, and supportive legislative frameworks. Practical measures like incentivizing large-scale biopolymer production, enforcing strict legislation toward petroleum-derived single-use plastics, and fostering interdisciplinary collaboration are crucial to effectively addressing these barriers.

In the near future, we could see the adoption of improved biopolymer properties by focusing on modern technologies such as advanced materials engineering, improved production efficiency, and the exploration of new raw materials. The coming opportunity may be particularly favorable for sources derived from microorganisms and insects. Emphasis should also be placed on leveraging bio-nanotechnology, genetic engineering, and innovative recycling technologies to further advance biopolymer sustainability and performance. A multidisciplinary approach, integrating biotechnology, materials science, economic analysis, environmental policy, and industrial applications, will be essential to fully harness the benefits and overcome the limitations identified throughout this chapter.

Ultimately, the strategic integration of biopolymer innovations into global sustainability agendas holds significant promise for reducing the environmental impacts associated with conventional plastics. Continued investment in research, strengthened policy measures and enhanced global cooperation will be essential to accelerate this transition, ensuring that biopolymer solutions become impactful globally while remaining adaptable to regional and local contexts.

8 Key Findings

• Growing Industry Adoption

The global food industry is increasingly integrating biopolymers as sustainable alternatives to conventional plastics, driven by environmental concerns, resource depletion, evolving consumer preferences for sustainable products, and tightening global regulations on packaging waste.

• Ongoing Technical and Economic Challenges

Despite their potential, the widespread adoption of biopolymers is hindered by significant challenges related to material processing, mechanical performance, barrier effectiveness, and cost competitiveness. These factors limit their industrial scalability and broader market penetration.

• Role of Bio-nanocomposites

Bio-nanocomposites have emerged as essential innovations, effectively addressing intrinsic limitations associated with conventional biopolymers. These advanced biodegradable materials demonstrate improved mechanical strength, enhanced thermal stability, and superior barrier properties, making them highly suitable for sustainable food packaging applications.

• Advances in Carbon-Based Nanomaterials

Recent innovations in carbon-based nanomaterials—such as carbon dots (CDs), carbon nanotubes (CNTs), and graphene—have substantially expanded the functionality of biopolymers. Notably, carbon dots derived from lactic acid bacteria offer outstanding antibacterial activity, chemical stability, and UV protection, enabling the development of active and intelligent food packaging solutions.

• Enhanced Properties Through Carbon Nanotubes

Incorporating single-walled and multi-walled carbon nanotubes into biopolymer matrices has significantly improved their mechanical, thermal, and antimicrobial properties. These enhancements underscore the potential of carbon nanotube-biopolymer composites for use as advanced, sustainable food preservation and packaging materials.

• Importance of Interdisciplinary Research

Continued interdisciplinary collaboration and innovation, particularly in biotechnology, material science, biotechnology, economics, and environmental policy, are critical to overcoming existing barriers. Such integrated approaches are essential for improving economic viability and facilitating large-scale industrial adoption of biopolymer-based food packaging solutions.

9 Call to Action

Encouraging greater investment in research, supportive policymaking, and broader industry adoption of biopolymers is essential to achieving global sustainability objectives. The biopolymer market is projected to grow significantly—from approximately USD 19.46 billion in 2024 to USD 40.67 billion by 2031—primarily driven by rising environmental concerns associated with petroleum-based polymer waste and increasingly stringent global regulations.

This global shift toward sustainability and stricter governmental policies to reduce single-use plastics will continue driving demand for biodegradable, recyclable, and compostable materials. Consequently, intensified investment in research and development is necessary to stimulate innovation in biopolymer production technologies, diversify sustainable feedstock sources, and expand practical applications in food production and eco-friendly packaging. Companies and investors must recognize biopolymers as strategic components of future packaging solutions, actively contributing to the global circular economy and sustainability goals.

However, the successful transition toward widespread biopolymer adoption faces several critical challenges, including the selection and optimization of materials with optimal performance characteristics, achieving economically viable mass production processes, enhancing biodegradation and recycling technologies, and converting waste streams and by-products into commercially valuable biopolymer materials. Addressing these barriers requires coordinated efforts involving researchers, industry stakeholders, policymakers, and consumers. Targeted financial incentives, supportive regulatory frameworks, industry collaboration, and public–private partnerships will accelerate biopolymer market integration and facilitate a sustainable global transition.

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Chapter 14

Biopolymers in Food Packaging

Materials: Challenges and Opportunities

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Abstract As the world's population continues to expand and lifestyle becomes increasingly industrialized, ensuring efficient food production, effective packaging, and maintaining quality standards have become critically important. Proper food packaging aims to reduce spoilage and extend shelf life. Most packaging materials, which are petroleum-based and derived from its byproducts, generate non-degradable waste, leading to pollution of water, air, and soil, as well as the production of greenhouse gases. As environmental concerns increase, there is a stronger shift toward natural biopolymers as replacements for industrial polymers. Natural biopolymers are highly valuable due to their biodegradability, environmental compatibility, antimicrobial properties, and high strength, attracting significant attention from researchers and scientists today. Biopolymers are derived from diverse sources such as plants, animals, and microbes, and they find applications in a wide range of industries, such as agriculture, medicine, pharmaceutical production, and packaging solutions. Among the challenges of using biopolymers in industry are their expensive production processes, material weaknesses, and the demand for improving their mechanical strength and thermal characteristics. Nevertheless, scientists are addressing these functional issues through various methods, such as blending biopolymers with each other, incorporating nanomaterials, and other innovative approaches. Therefore, in numerous fields, especially within packaging applications, the use of biopolymers and new technologies can create sustainable and innovative opportunities to enhance the safety, quality, and shelf life of food items while minimizing waste generation.

Keywords Polymer · Biopolymer · Biodegradability · Antimicrobial properties · Food packaging

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1 Introduction

Today, with the exponential rise in the global population and escalating food requirements, competition in the field of efficient food production and ensuring its safety is intensifying [1]. Urban life and industrial developments today, along with their impact on people's lives, have highlighted the importance of providing safe and high-quality food. In general, food packaging serves a vital role in this aspect, as optimal packaging supports the quality and nutritional retention of food, reduces physical and chemical spoilage, and minimizes contamination, dust, and physical damage to food products [2].

According to reports from the Centers for Disease Control and Prevention (CDC), approximately 48 million foodborne illnesses occur annually in the United States, with a significant proportion affecting children below the age of 15. This imposes significant costs on the healthcare sector and, in some cases, unfortunately, leads to patient fatalities [3]. To tackle these challenges and mitigate food spoilage and the risk of pathogens, materials like glass, plastic, and paper are widely employed in packaging to prolong the shelf life of food products [4]. Recently, the packaging industry has increasingly prioritized polymer-based materials due to their beneficial characteristics, such as lightweight design, resistance to thermal and mechanical stress, corrosion resistance, and ease of manufacturing [5]. Polymers are widely used as structural materials in packaging because of their stability and versatility, which allow them to meet diverse functional needs [6]. Another advantage of using polymers in food packaging is their ability to incorporate various additives, such as antimicrobial, anti-mold, and anti-fungal agents, as well as oxygen absorbers, which enhance food storage capabilities [7].

Therefore, due to their distinctive features—such as affordability, durability, and versatility—polymers have become an essential part of modern industrial life. As a result, the production of polymer-based products and packaging continues to grow annually, driven by increasing demand and global population growth. Nearly 99% of these polymers are derived from petrochemical sources, relying on non-renewable fossil fuels [8]. The packaging sector accounts for approximately 43% of global plastic production [8]. However, the manufacturing and treatment of plastics are highly energy-intensive, contributing substantially to the release of greenhouse gases and exacerbating climate change (Fig. 1). Such emissions pose serious risks to both ecological systems and human health [9].

Moreover, the incineration of plastics releases toxic substances, including carbon monoxide, chlorine, hydrochloric acid, dioxins, furans, and hazardous compounds like benzene, styrene, and acetaldehyde [10]. Beyond air pollution, plastics generate vast amounts of non-biodegradable waste, which persists in the environment and contaminates soil and water through the leaching of harmful chemicals [11]. The non-biodegradable nature of conventional plastics has made waste management a pressing and unresolved issue for decades, highlighting the urgent need for sustainable alternatives [12].

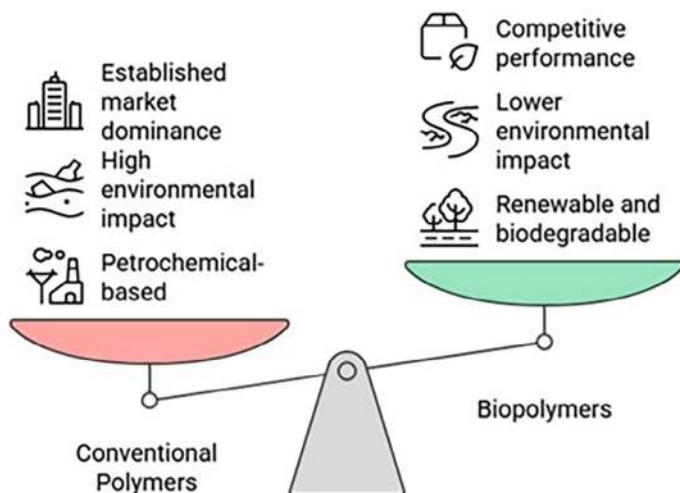


Fig. 1 Comparing conventional and biopolymer packaging applications

To address the issues caused by synthetic polymers used in various industries, biopolymers derived from natural sources are being utilized. These biodegradable materials are also suitable for applications in the packaging industry [13]. Therefore, biopolymers serve as suitable alternatives to petroleum-based polymers. In addition to being environmentally friendly and biodegradable, these materials possess significant physical and functional properties that allow them to compete effectively with petroleum-based polymers [14].

2 Applications of Biopolymers in Different Industries

Because of their exceptional characteristics and eco-friendly attributes, biopolymers are widely used in various fields, not only in the packaging industry but also in other industries, including pharmaceuticals, medicine, agriculture, and more, as briefly mentioned below.

- **Medical and Pharmaceutical Industry**

Among the biodegradable biopolymers used in the medical and pharmaceutical industries, chitosan, collagen, and polylactic acid (PLA) are notable examples. These biopolymers are effectively utilized in drug delivery mechanisms, wound healing, biomaterial engineering, and surgical sutures [15].

- **Agriculture**
- Biopolymers are utilized in the agricultural industry, particularly in smart fertilizer systems with controlled-release capabilities and seed coating. These applications

lead to improved soil performance and, more importantly, enhance soil health and prevent soil degradation, ultimately contributing to sustainable and efficient agriculture [16].

- Textile Industry

In the textile and apparel industry, biodegradable biopolymers such as cellulose and polylactic acid (PLA) are primarily used to produce sustainable fibers and fabrics. As biodegradable materials, they help reduce the environmental footprint of the textile industry [17].

- Packaging Industry

In general, one of the main uses of biopolymers is in packaging, where they aim to reduce environmental pollution. They are primarily utilized in food packaging, carrier bags, and disposable containers [17].

- Automotive Industry

In the automotive industry, biopolymers are used to produce modern vehicles with lighter weights, lower fuel consumption, and higher efficiency, ultimately leading to a reduced environmental impact [18].

3 Taxonomy of Biodegradable Polymers

In packaging, numerous natural and synthetic biodegradable biopolymers are applied, which can be classified based on various criteria, including environmental impact, biological origin, and reliance on fossil resources [9]. They typically fall into three types: synthetic, natural, and those produced or modified by microorganisms (Fig. 2) [19]. These polymers degrade into natural residues (biomass), water, CO₂, and inorganic compounds when they break down; additionally, they contribute to humus formation [20].

In addition, biodegradable polymers can be distinguished from reusable polymers. A compostable polymer is a polymer that fully decomposes and disintegrates within six months without releasing dangerous residues into nature. However, this characteristic is crucial for environmental integrity and supports the practice of sustainable waste management [21].

3.1 Natural Polymers

Natural-based substances, referred to as natural polymers, are extracted through physical or chemical methods from natural sources. Considering their chemical composition, these polymers are categorized into three primary classes: (i) polysaccharides, (ii) proteins, and (iii) polyesters. Examples of natural polymers include cellulose,

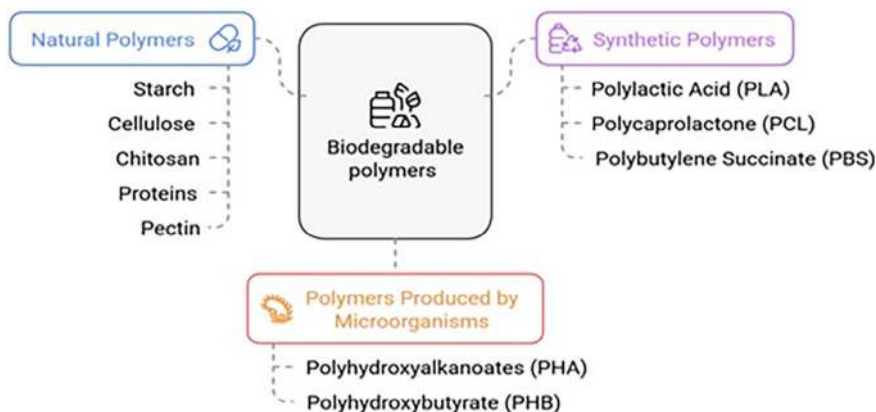


Fig. 2 Different classifications of biopolymers by their source

starch, proteins, wool, silk, and DNA. These materials have been widely applied in food production, textiles, paper manufacturing, wood processing, adhesives, and pharmaceuticals [22].

Gelatin, alginate, fibrinogen, and hyaluronan are naturally occurring polymer that is soluble in water and can be dissolved in biocompatible inorganic solvents such as phosphate-buffered saline and cell culture media to form solutions or hydrogels [23]. The physical, thermal, structural, and protective properties of these polymers are used to evaluate their quality [24].

In recent years, researchers have been interested in developing sustainable products from eco-friendly and decomposable substances. Natural polymers are inherently biodegradable, as their degradation pathways involve enzymes, and their biological origins make them environmentally friendly [25]. Natural polymers are more environmentally friendly, biocompatible, and less harmful than synthetic polymers. Moreover, they have several useful characteristics, including antioxidant and antimicrobial functions, alongside improved nutritional quality in food uses, and cost-effectiveness. Natural polymers do not have harmful environmental impacts like inorganic plastics do [26].

3.1.1 Starch

Starch, a polysaccharide derived from plants, such as corn, wheat, rice, and potatoes, is a biodegradable, renewable, and cost-effective polymer widely utilized in multiple sectors, such as food packaging, drug delivery, and water purification. Starch is structurally composed of two major glucose-based polymers, amylose and amylopectin, joined by glycosidic bonds, with an amylose **composition** of 10–20% and amylopectin **composition** of 80–90%, depending on the source [22]. Native

starch is abundant and sustainable, but it is brittle, hydrophilic, poorly processable, and does not possess sufficient mechanical or barrier properties for packaging applications [27].

To overcome these limitations, various modification strategies have been developed. For example, improving thermal and structural characteristics through chemical modifications (e.g., hydrolysis and succinylation) and physical techniques (reactive extrusion, electrospinning, and 3D printing) enhances the functional versatility of starch [28]. Dual treatment of corn starch using acid hydrolysis and succinylation has been shown to significantly decrease viscosity, gelatinization enthalpy, and pasting temperature, making it more suitable for industrial processes [29]. Furthermore, mechanical properties can be enhanced, and water sensitivity reduced, by the addition of plasticizers, nanoparticles, or other polymers [30]. Recent advances include the use of β -amylase treatment to reduce retrogradation in wheat starch as well as adding stearic acid to alter rice starch rheology and 3D printing characteristics to develop V-type crystalline structures [31]. These developments emphasize the promise of starch as a sustainable foundational material for high-performance biodegradable packaging solutions, furthering its purpose as a critical component in the transition to environmentally friendly materials [32].

3.1.2 Cellulose

Cellulose, the most abundant natural biopolymer globally, is derived from plant-based sources like cotton and wood, and cereals, as well as microorganisms including bacteria, algae, and fungi. Its molecular structure consisting of straight chains of D-glucose monomers joined by β -1,4 glycosidic linkages, with functional hydroxyl groups that facilitate extensive hydrogen bonding. This unique structure grants cellulose exceptional physicochemical properties such as renewability, biodegradability, economic viability, and high mechanical durability. Nevertheless, its high crystallinity, hydrophilicity, and insolubility in water present challenges for direct application in film production and food packaging [33].

To overcome the limitations of cellulose, scientists have adopted various approaches, such as embedding nanoparticles like silver, zinc oxide, and copper oxide into cellulose derivatives, including carboxymethyl cellulose (CMC) and hydroxypropyl methyl cellulose (HPMC). This has resulted in enhanced tensile strength, reduced moisture permeability, and improved antibacterial properties of cellulose [34]. Additionally, cellulose can further enhance its functional and inhibitory properties by being combined with chitosan [35].

Cellulose produced by microorganisms (BC), compared to plant cellulose, possesses superior properties such as high purity, crystallinity levels of up to 95%, and mechanical strength (Young's modulus up to 114 GPa), and is primarily produced by *Acetobacter xylinum* [36]. Among the other capabilities and superior features of bacterial cellulose compared to plant cellulose are its extremely high biocompatibility and its remarkable ability to polymerize, which can sometimes exceed 16,000 times its own weight. This characteristic offers promising potential for the application of

this type of cellulose in smart packaging containing antioxidant and antimicrobial agents [37]. Conversely, films derived from cellulose exhibit superior barrier capabilities against gases, lipids, and salts. This characteristic ensures the preservation of food quality and color, while also preventing the growth of microorganisms during storage [34]. Generally, cellulose films exhibit greater resistance to water and fats, and their tensile strength is higher compared to other cellulose derivatives. This has broadened their use in manufacturing food packaging materials [38]. These characteristics, along with the outstanding properties of cellulose and its derivatives, have significantly enhanced the role of this compound in the packaging industry [39]. By leveraging cellulose's inherent properties and employing advanced modification techniques, cellulose-based materials can meet the increasing demand for sustainable materials within the food packaging sector. Future work should investigate the optimization of these materials for industrial-scale manufacturing and explore further improvements in their functionalization to enhance performance.

3.1.3 Chitosan

Chitosan ranks as the second most plentiful polysaccharide, following cellulose, making it an environmentally degradable, non-hazardous, and biocompatible biopolymer extracted from crustacean shells, predominantly derived from shrimp and crab through the deacetylation of chitin. Its molecular structure consists of α 1,4 or α 1,4 bis-D-glucosamine and N-acetyl- α 1,4-bis-D-glucosamine units [40]. Chitosan exhibits excellent film-forming properties, microbial inhibition against bacteria, molds, and yeasts, and poor oxygen permeability, positioning it as a perfect choice for use in food packaging. However, its poor mechanical characteristics, high hygroscopicity, and moisture sensitivity limit its practical use [41, 42].

To resolve these issues, researchers have developed various modification techniques. Tensile strength, the water vapor permeability (WVP) and barrier characteristics can be enhanced by combining chitosan with additional biopolymers [43], and embedding nanoparticles (e.g., montmorillonite nanoclay) [44], or reinforcing it with graphene oxide [45]. Additionally, the addition of bacterial cellulose nanocrystals to chitosan matrices enhances crystallinity and reduces water permeability while maintaining excellent transparency [46]. These advancements highlight chitosan's capability as an eco-friendly, versatile material for sustainable food packaging solutions, offering antimicrobial protection and enhanced mechanical and barrier properties [47]. **Additional** studies should focus on enhancing these composites for industrial-scale production and expanding their applications within the food sector.

3.1.4 Proteins

Biodegradable and highly functional materials, natural polymer proteins are used in novel composite and blended material development. The existence of these proteins in both globular or fibrous forms, and their chemical and physical characteristics are

determined by the specific types and locations of amino acid structures within the polypeptide chain. Proteins are classified based on their chemical structure into whey protein, zein, gluten, and soy protein [48]. In food coating, protein-based films are used to coat fruits, vegetables, nuts, meat, and ready-made desserts, and as well as separating food layers [49]. Polymers derived from proteins have been investigated for applications in both food and non-food packaging, along with their potential in healthcare. Whey proteins serve as excellent starting materials for creating edible and environmentally sustainable packaging because they are flexible and can form biodegradable films. With their favorable properties, such as high oxygen barrier capacity and excellent biodegradability, they are a strong candidate for sustainable packaging [50]. Corn endosperm-derived zein protein exhibits gas barrier, biodegradability, and biocompatibility properties and is therefore a good protective coating for food packaging. Zein-based films are combined with additional polymers to enhance their resistance to gas, light, and moisture, while also boosting mechanical strength and antibacterial properties, ultimately extending the shelf life of food items [51].

Wheat gluten is an economically viable and widely accessible by-product of starch production. It has a very high degradation rate relative to other polymers and produces no toxic by-products. Wheat gluten has outstanding film-forming properties and is often used in biodegradable materials, but its brittleness requires the addition of plasticizers [52].

Soy protein isolate contains approximately 70% protein and is devoid of water-soluble carbohydrates. Structural modification of soy protein concentrate results in textured soy protein (TSP). Nevertheless, TSP-based films suffer from weak structural and protective characteristics because of their hydrophilic nature. Like films of isolated soy protein, films created using isolated soy protein are also quite prone to water absorption [53]. Research shows that the heat and stretch characteristics of these films are improved by blending in 25% stearic acid; the moisture sensitivity is lessened [54]. Incorporation of plasticizers such as glycerol, gellan gum, or κ -carrageenan has been studied to develop biodegradable soy protein packaging materials, such as trays [55].

3.1.5 Pectin

Pectin is a well-characterized, multifunctional biopolymer utilized as a stabilizer and gel-forming agent in numerous food-related uses. It is a major element of plant cell walls and is extensively extracted for use in food formulations and packaging systems. Pectin is classified under the EU code E440 and is applied in the manufacturing of jams, jellies, fruit juices, sweets, pastry fillings, and food packaging materials [56].

While pure pectin films are functional, they suffer from a number of limitations, such as low tensile strength, high hydrophilicity, and brittleness, which limit their use in packaging [57]. The films are enhanced by incorporating various biopolymers to improve flexibility and structural integrity [58]. The molecular structure of pectin also has a pronounced effect on its mechanical behavior, with highly branched pectin displaying higher tensile strength as a result of greater molecular entanglement [59].

WVP is a significant packaging material factor, which influences food-quality preservation. Pectin films exhibit inherently high water solubility and moisture absorption capacity but have poor barrier properties. However, they are resistant to moisture transfer, and structural modifications or hydrophobic agents can be added to enhance their moisture transfer resistance [60]. In addition, pectin-based films inherently have no strong antibacterial properties; however, the integration of bioactive compounds can enhance antimicrobial properties, prevent the growth of microorganisms and slow down lipid oxidation, and regulate moisture migration, as a result, enhancing the shelf life of packaged foods [61].

3.2 *Synthetic Polymers*

Bio-based polymers synthesized via conventional chemical methods are eco-friendly and sustainable materials derived from natural sources and processed through polymerization techniques to obtain high-performance engineering compounds. These polymers are used across various sectors, including packaging, medical applications, and even advanced material manufacturing, on account of their excellent mechanical properties, biodegradability, and low dependence on fossil-based resources [62, 63]. The development of such materials represents a significant step towards minimizing environmental impact and promoting sustainable technologies in the polymer industry [64]. Among synthetic polymers, the following are notable:

3.2.1 **Polylactic Acid (PLA)**

Polylactic acid (PLA) is produced through the ring-opening polymerization process of lactide monomers derived from sustainable sources via fermentation, including corn and sugar. PLA is both heat- and water-degradable and is referred to as a biodegradable and compostable plastic. It is highly significant because it is environmentally friendly, recyclable, and compostable, making it appropriate for various food packaging applications. The features of PLA can be controlled from amorphous to crystalline by adjusting the monomeric ratio, and they include mechanical strength, degradation rate, and thermal properties [6, 65].

Commercial PLA has a glass transition temperature of about 63°–63.8 °C, and its crystallinity is important for its degradation behavior: highly crystalline structures degrade more slowly. The good mechanical properties of PLA include high molecular weight, water insolubility, and ease of processing by molding techniques such as injection, extrusion, blowing, thermoforming, and film production. Furthermore, it possesses barrier characteristics comparable to polyethylene (PE), PET, and polystyrene, and is therefore a good candidate for short-shelf-life food packaging, trays, and coatings on paper-based materials [66].

Furthermore, PLA can be chemically recycled into lactic acid and re-polymerized, making it more sustainable. However, despite these advantages, unmodified PLA has

some weaknesses, like brittleness and reduced stability at high temperatures, and thus it must be blended with other biodegradable polymers for better performance [67].

3.2.2 Polycaprolactone (PCL)

PCL is a semi-crystalline, entirely environmentally degradable, and low-cost, petroleum-derived polymer with good processability. The glass transition temperature is about -60°C , and it dissolves in a range of organic and inorganic solvents, which makes it highly suitable as a stabilizer in polyurethane formulations [68]. Hydrophilic chitosan is added to PCL to improve the inherent water-repellent nature of the mixture. Furthermore, the composite displays a lower water vapor transmission rate (WVTR) than pure films, which helps increase the longevity of food products stored in such packaging (69). Commercially, PCL is sold as Tone® (Union Carbide), Celgreen® (Daicel), and CAPA® (Solvay) [69].

3.2.3 Polybutylene Succinate (PBS)

The polyalkenedicarboxylate group encompasses polybutylene succinate (PBS), created through the polycondensation of 1, 4-butanediol and ethylene glycol with adipic and succinic acid. The white, crystalline PBS polymer exhibits excellent processing performance, with a glass transition temperature ranging from -45°C to -10°C , and its phase transition temperature ranges from 90°C to 120°C . The material stretches significantly (up to 330%) before breaking, and its mechanical properties match those of polyethylene (PE) and polypropylene (PP) [70, 71]. Showa Denko launched Bionolle® PBS as the first material under the PBS category in Japan in 1990.

The original PBS development led to the synthesis of PBSA through the addition of adipic acid in controlled amounts, resulting in the production of polybutylene succinate-co-adipate (PBSA) [72]. The inclusion of small amounts of coupling agents increases the molecular weight of PBS [71]. The company SK Chemicals in South Korea developed Skygreen® as one of the many commercial PBS versions through monomer composition modifications. The choice of diols and dicarboxylic acids during polymerization directly influences both the physical characteristics and degradation speed of these polymers [71].

3.2.4 Polylactide Aliphatic Copolymer (CPLA)

The production of CPLA begins with combining lactide, a renewable material, with dicarboxylic acid to form an aliphatic polyester. The material properties of CPLA match those of polypropylene and polystyrene, depending on the amount of polyester present in the blend. The heat resistance of CPLA extends up to 200°C [73]. The combustion process of CPLA produces fewer carbon dioxide emissions (CO_2) than

both polyethylene (PE) and polypropylene (PP). The incineration of CPLA does not produce any toxic substances during the process. The degradation process of CPLA starts approximately two weeks after it comes into contact with food. In natural environmental conditions, degradation takes five to six months, with total decomposition completing within twelve months [74]. The Japanese firm Dainippon Ink Chemicals produces CPLA film under the trademark CPLA™ for commercial use [73].

3.2.5 Polyglycolide (PGA)

Polyglycolide synthesis occurs through the polycondensation process of glycolic acid, creating a material known as polyglycolic acid (PGA) [75]. Polyglycolide is one of the primary essential aliphatic polyesters because it transitions into a glassy state between 35 and 40 °C and has a melting temperature between 220 and 250 °C [76]. The high crystallinity content of 40–55 % in PGA makes the material insoluble in water, while allowing easy dissolution in most fluorinated solvents to produce high-molecular-weight polymer films. Biological organisms absorb the entire polymer within a 5–6-month timeframe. PGA products available on the market include Kurudex™, developed by Kureha Chemical Industries specifically for food packaging applications. The Chemours Company operates a facility that manufactures low-molecular-weight PGA film [77].

3.2.6 Polybutylene Adipate-Co-Terephthalate (PBAT)

The production of PBAT (polybutylene adipate terephthalate) occurs through the chemical condensation reaction between 1,4-butanediol, terephthalic acid, and adipic acid [78]. The properties of PBAT improve as the quantity of terephthalic acid surpasses 35 mol%. When the concentration exceeds 55 mol%, the rate of PBAT biodegradation decreases [79]. The soft and flexible characteristics of PBAT match those of PCL, which enables its use in film-making, filament manufacturing, bottle production, and product molding applications. The material can be combined with cellulose and starch, together with various biodegradable polymers. The combination of PBAT with cellulose materials improves both hydrophobicity and mechanical properties while enhancing thermal properties [80]. The addition of PBAT to PHBV systems leads to reduced crystallinity levels [81]. The PBAT market contains products from BASF under the Ecoflex™ name, alongside Origo-Bi™ from Novamont and Easter Bio™ from Eastman Chemical [78].

3.2.7 Polyvinyl Alcohol (PVA)

The semi-crystalline polymer PVA consists mainly of amorphous phases, yet contains a small crystalline component. The chemical structure of poly(vinyl acetate) includes

1,3-diol or 1,2-diol units that vary according to the level of hydrolysis during its production. The molecular weight of PVA, together with its degree of hydrolysis, determines most of its properties. The polymerization length of vinyl acetate chains in PVA determines its typical weight range of 20,000 to 400,000. The degree of hydrolysis typically falls between 80 % and 99 % [82].

3.2.8 Polypropylene Carbonate (PPC)

Polypropylene carbonate (PPC), a type of aliphatic polycarbonate, is synthesized by copolymerizing carbon dioxide (CO₂) and propylene oxide. PPC-based films exhibit superior tensile strength and better water (H₂O) and oxygen (O₂) barrier performance compared to PBAT, LDPE, and polyethylene/starch blends. The mechanical stability of PPC films is lower than that of PBAT but surpasses both LDPE and polyethylene/starch composites [83]. The amorphous structure of PPC presents multiple disadvantages, as it leads to poor thermal durability, substantial dimensional changes, and weak physical properties, alongside a lower T_g range of 25–45 °C [79]. The actual performance attributes of PPC change dramatically based on the catalyst used during its manufacturing process [83].

3.3 *Polymers Synthesized by Natural and Genetically Modified Microorganisms*

The group 3 polymers represent bio-based materials that microorganisms and genetically engineered bacteria produce. The leading members of this group are the polyhydroxyalkanoates (PHAs), which serve as microbial energy reserves in diverse species. Scientists continue to expand their research by investigating new biopolymers within the Group 3 category, including bacterial cellulose and novel polysaccharides. The expansion of sustainable materials science is driven by rising interest in polymeric materials that serve various purposes across biomedical fields and packaging applications [84]. The ability of microorganisms to tailor specific properties positions this group as a leading candidate for the development of environmentally friendly plastic substitutes.

3.3.1 Polyhydroxyalkanoates (PHA)

The bacterial fermentation process produces polyhydroxyalkanoates (PHAs), which are natural polymeric compounds derived from substrates such as sugars, glucose, and vegetable oils. The biopolymer family has received substantial interest due to its biodegradable nature, which makes it suitable for food packaging applications [83]. Bacteria produce PHAs as energy storage compounds within their cells, where these

compounds can constitute between 30% and 80% of the cell's dry weight when bacteria experience nitrogen limitation under carbon-rich conditions. The melting temperature (T_m) of PHAs ranges from 40 to 180 °C, depending on the monomers used during production. PHA materials display adjustable mechanical properties, which enable the fabrication of materials with variable stiffness, ranging from brittle to rubber-like, based on the selected carbon source and microbial strain [79]. Scientists have shown that PHA functions more effectively as a barrier when combined with zein, which originates from plants. The combination of PHA and zein alters permeability, resulting in a 39–48 % reduction in water vapor transmission and a 27–35 % decrease in oxygen permeability [83]. The addition of zein modifies the blend structure, while simultaneously improving its functional attributes. PHAs are fully biodegradable due to the action of esterase enzymes, which degrade the polymer by breaking the ester bonds connecting the monomers [79].

3.3.2 Polyhydroxybutyrate (PHB)

Polyhydroxybutyrate (PHB) is the leading member of the polyhydroxyalkanoate (PHA) family because it forms via the polymerization of 3-hydroxybutyrate units [85]. PHB stands out for its superior UV resistance and light transmission characteristics, as it has a T_m of 180 °C and a T_g of 55 °C. The material exhibits exceptional crystalline organization, with crystallinity levels exceeding 50 %. However, its thermal stability deteriorates as the temperature approaches or falls below its melting point [86]. The processability of PHB suffers a severe decline when subjected to temperatures that are 10 °C lower than its T_m [87]. Researchers have investigated three approaches to improve PHB performance: copolymerizing it with other alkanoates, adding biodegradable additives, and blending it with secondary polymers. These approaches allow the creation of products with varying structural compositions as well as mechanical attributes [88]. The biodegradable nature of PHB is particularly notable, as many microbial organisms (e.g., bacteria, fungi, algae) can decompose it effectively under different environmental conditions. The hydrolytic breakdown of the material transforms it into 3-hydroxybutyric acid, although the process occurs at a moderate rate [89].

3.3.3 Polyhydroxybutyrate-Valerate (PHBV)

The production of PHBV copolymer requires the use of propionic acid in the fermentation feedstock. The incorporation of propionic acid transforms the material into a flexible substance, which outperforms its homopolymer form in packaging applications [90]. Under conditions of high microbial activity, PHBV degrades within a period of five to six weeks. The degradation process in the presence of oxygen produces both CO₂ and water (H₂O), but under anaerobic conditions, it leads to faster degradation and generates methane as a result [91].

Table 1 provides an overview of the advantages and limitations of biopolymers, along with practical approaches to overcome these limitations.

4 Advantages of Biopolymers in Food Packaging

4.1 Environmental Compatibility and Biodegradability

Biopolymers are macromolecules produced from natural sources through enzymatic or chemical methods. They decompose via microbial activity and enzyme action into smaller fragments, which are further broken down into monomers until they ultimately transform into end products such as CO₂, CH₂, and H₂O [109, 110]. The complete biodegradation process involves several stages: biodeterioration, depolymerization, bio-assimilation, and finally mineralization. Biodegradation can occur aerobically, utilizing oxygen to produce CO₂, or anaerobically, generating CH₂ in the absence of oxygen. Both biotic factors (e.g., microorganisms like bacteria and fungi) and abiotic factors (e.g., temperature, light, mechanical stress) influence the degradation process [111]. The mechanical properties of biopolymers are weakened by processes such as hydrolysis, photodegradation, and thermo-oxidative degradation [112]. Figure 3 represents different advantages of utilizing biopolymer materials for food packaging applications.

Biopolymers have gained popularity in food packaging applications, such as salad cups and disposable cutlery, due to their environmental benefits. Life-cycle assessments (LCAs) are frequently employed to assess the ecological effects of these materials; however, they often fail to account for social and economic impacts [14]. The stability of biopolymers can be enhanced by incorporating synthetic materials during modification processes. In the final stage of the life cycle of biopolymers, these compounds are broken down by microorganisms in the soil and converted into water, carbon dioxide, and biomass [14]. However, the challenge facing scientists is addressing the questions and concerns associated with the environmental and economic impacts of using biopolymers in various industries.

4.2 Reduction of Carbon Footprint

Biopolymers contribute substantially to lowering carbon emissions and mitigating air quality degradation. For instance, biopolymers such as PLA and PHA act as eco-friendly substitutes for conventional plastics derived from petroleum [111]. The entire lifecycle of biopolymers generates significantly fewer greenhouse gas emissions than traditional plastics, thereby helping to alleviate global warming [14]. In contrast, petroleum-based plastics release substantial amounts of pollution during production and use, with packaging-related products contributing significantly to

Table 1 Advantages and limitations of various biopolymers

Biopolymer	Positive characteristics	Negative characteristics	Solutions	Applications	References
Starch	Biodegradable, renewable, non-toxic	Brittleness, moisture sensitivity	Chemical modification, mixing with plasticizers	Food packaging, biodegradable films	[92]
Cellulose	Biodegradable, good mechanical properties	Limited barrier properties, high cost	Nanocomposite formation, mixing with additional biopolymers like PLA and PHBV	Coatings, food packaging	[93]
Chitosan	Biodegradable, antimicrobial properties	Poor mechanical strength, high moisture sensitivity	Reinforcement with nanofillers	Antimicrobial packaging, food preservation	[94]
Protein	Biodegradable, good film-forming ability	Poor water resistance, variable mechanical properties	Crosslinking, mixing with additional biopolymers like starch, chitosan, PLA	Edible films, food packaging	[92, 95]
Pectin	Biodegradable, gelling properties	Limited mechanical strength, moisture sensitivity	Mixing with additional biopolymers like starch, chitosan	Food coatings, biodegradable films	[56, 94]
Wheat Gluten	Biodegradable, good film-forming properties	Poor barrier properties, sensitivity to moisture	Mixing with hydrophobic materials	Food packaging, biodegradable films	[96]
Soy protein	Biodegradable, good film-forming ability	Poor water resistance, variable mechanical properties	Crosslinking, mixing with additional biopolymers like chitosan, starch, alginate	Food packaging, biodegradable films	[49, 97]
PLA	Biodegradable, good mechanical properties	Brittle, sensitive to heat	Mixing with additional biopolymers like PHB, PBS, copolymerization	Food packaging, disposable cutlery	[98, 99]
PCL	Biodegradable, flexible, good mechanical properties	High cost, slow degradation rate	Mixing with additional biopolymers like PLA, PHBV, chitosan	Controlled release systems, packaging	[100, 101]

(continued)

Table 1 (continued)

Biopolymer	Positive characteristics	Negative characteristics	Solutions	Applications	References
PBS	Biodegradable, good thermal stability	Limited mechanical properties	Mixing with additional biopolymers like PLA, PCL	Food packaging, disposable items	[99, 102]
PHA	Biodegradable, good mechanical properties	High production cost	Biotechnological advancements, optimizing production	Food packaging, agricultural films	[95]
PHB	Biodegradable, good mechanical properties	Brittle, high production cost	Mixing with additional biopolymers like PLA, cellulose Nano crystals	Food packaging, biomedical applications	[103, 104]
PHBV	Biodegradable, good mechanical properties	High production cost	Biotechnological advancements, optimizing production	Food packaging, agricultural films	[93]
PVA	Biodegradable, good film-forming ability	Poor water resistance, high cost	Mixing with additional biopolymers like cellulose, chitosan, starch	Water-soluble films, packaging	[13, 105, 106]
PBAT	Biodegradable, good flexibility	High cost, limited mechanical properties	Mixing with additional biopolymers like PLA and PBS	Food packaging, compostable bags	[107, 108]
PPC	Biodegradable, good mechanical properties	Limited availability, high cost	Research on production methods	Food packaging, biodegradable films	[95]
PHA	Biodegradable, good mechanical properties	High production cost	Biotechnological advancements, optimizing production	Food packaging, agricultural films	[95]
PHB	Biodegradable, good mechanical properties	Brittle, high production cost	Mixing with additional biopolymers like PLA, cellulose nanocrystals	Food packaging, biomedical applications	[103, 104]

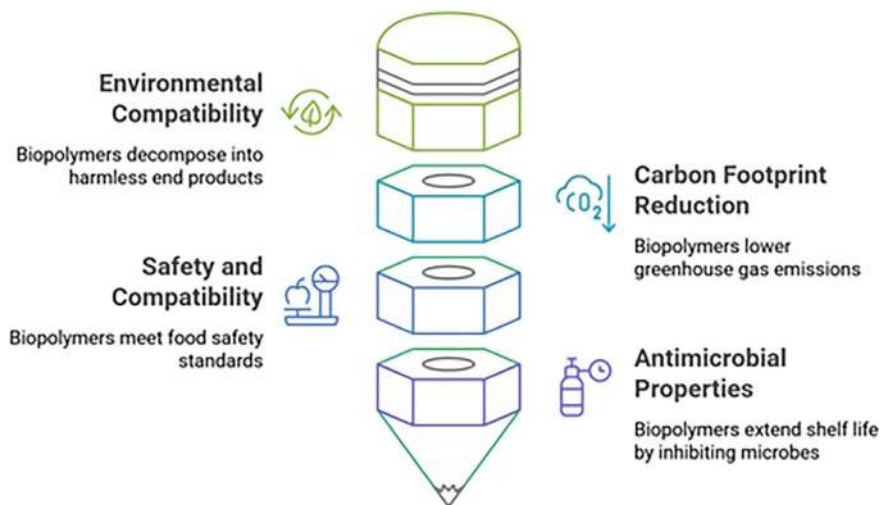


Fig. 3 Advantages of utilizing biopolymer materials for food packaging applications

greenhouse gas (GHG) emissions. Biopolymers offer a promising solution by minimizing both emissions and environmental impacts [113]. Nevertheless, biopolymers frequently need to be combined with other substances to enhance their thermal and mechanical performance, as they currently exhibit limitations in these areas. Such combinations can enhance their performance characteristics [92]. Replacing petroleum-based materials with biopolymers can lead to reduced carbon emissions and lower air pollution, provided that effective waste management systems are in place for end-of-life products [14].

4.3 Safety and Compatibility with Food Materials

Research shows that starch, chitosan, and PLA biopolymers are prominent choices for food packaging due to their ease of decomposition, sustainability, and food-friendly properties [92]. However, the primary concerns surrounding biopolymers are food safety and material compatibility. Food safety regulations mandate that biopolymers meet specific standards to prevent the release of harmful substances that could migrate into food. Special attention is required during the evaluation of additives used in biopolymer formulations, such as plasticizers and stabilizers, to avoid potential food contamination [93]. Honestly, most biopolymers lack sufficient mechanical strength and adequate barrier properties against environmental factors. Therefore, to address this issue, solutions such as mixing with other biopolymers, combining with antimicrobial agents, and incorporating antioxidant agents are used [93]. As a result, conducting effective research to address these issues and meet the necessary requirements to achieve high-quality and efficient packaging is essential.

4.4 Antimicrobial Properties and Extended Product Shelf Life

Biopolymers obtained from natural sources, like polysaccharides, proteins, and similar materials, are regarded as excellent options for food packaging because of their biodegradable nature and eco-friendliness [92, 114]. To enhance the efficiency of biodegradable biopolymers, they can be mixed with antimicrobial agents, such as plant essential oils and silver nanoparticles, for application in food packaging. Consequently, these compounds help reduce the growth of microorganisms and improve the safety of food products. For example, the application of silver nanoparticles within biopolymer-based films has shown significant antimicrobial effectiveness against bacterial species like *E. coli* and *S. aureus* [114].

To boost the antimicrobial and antioxidant capabilities of biopolymers, natural substances, like plant-derived essential oils, can be utilized as alternatives to synthetic compounds. This approach enhances the overall functionality of biopolymer materials [115]. These substances play a key role in protecting food items by inhibiting microbial growth and maintaining their quality and freshness. For instance, biopolymer-based films can slow down lipid oxidation and prevent spoilage thanks to their antioxidant and antimicrobial features, which help keep food fresh for longer periods [116]. Moreover, combining biopolymers with natural antimicrobial materials enhances the safety and shelf life of food products, making biopolymers a suitable option for producing sustainable packaging [117, 118].

5 Uses of Biopolymers in the Packaging Industry

As previously mentioned, biopolymers, due to their biodegradable nature and environmental compatibility, have been widely used in the packaging sector for various purposes, such as creating coatings, manufacturing food storage containers, developing protective layers, producing antimicrobial packaging, and designing trays for the food industry. At the same time, with the increased use and production of biopolymer-based products, the use and production of synthetic and industrial polymers have decreased, consequently lowering pollution caused by plastic consumption. Therefore, their adaptability and eco-friendly characteristics make them a promising solution for developing sustainable packaging systems across various industries (Fig. 4).

5.1 Edible Packaging

Another advantage of packaging using biopolymers is the combination of functional properties with environmental benefits. On one hand, it extends the shelf life of

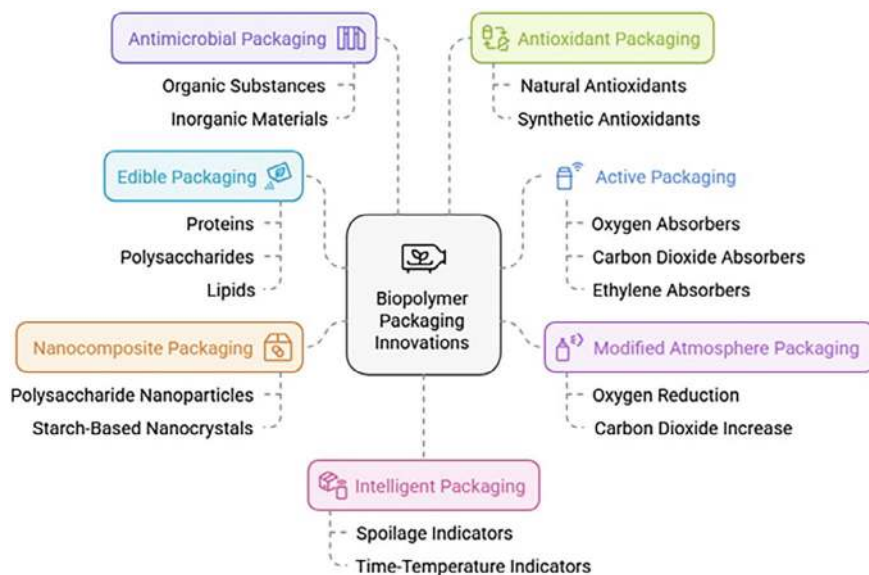


Fig. 4 Types of innovations in food packaging using biopolymers

food products, and however, since the packaging coating is consumable, it reduces the generation of waste and bio-waste [119]. The main components in edible packaging include films, coatings, sheets, and packages designed to protect food items, extend shelf life, and enhance sensory quality [120]. Packaging materials are derived from proteins, polysaccharides, and lipids, each providing unique characteristics to the packaging system. Edible packaging often relies on proteins such as gelatin, collagen, and chitosan, as these materials provide excellent protection against oxygen and moisture. Gelatin coatings effectively reduce oxygen permeability and prevent oil migration, while collagen-based films have gained commercial success as sausage casings due to their ability to enhance juiciness and reduce shrinkage in processed meats [121]. Polysaccharides, such as cellulose derivatives, chitosan, carrageenan, and alginates, are extensively utilized in the food sector because they form effective gas barriers and adhere well to food surfaces, making them ideal for preserving fruits and vegetables. However, the hydrophilic nature of these materials limits their ability to prevent moisture loss. Lipids, which are hydrophobic substances, are frequently blended with proteins or polysaccharides to enhance their ability to block moisture [122]. Edible packaging offers three essential benefits: antimicrobial protection, antioxidant functions, and moisture barrier properties, which protect food from light-induced chemical changes, microbial growth, and oxidation processes [123]. Edible packaging often works in tandem with non-edible packaging to enhance food preservation, as the latter provides additional protection against environmental threats and bacterial contamination. The development of edible packaging represents a significant breakthrough in preservation technology, offering a sustainable and functional

alternative to conventional packaging materials [124]. By combining the properties of proteins, polysaccharides, and lipids, edible packaging effectively preserves food products, extends freshness, and reduces environmental strain. Edible packaging is positioned to become a crucial component of sustainable food systems, with ongoing advancements in research and innovation [125].

5.2 *Modified Atmosphere Packaging (MAP)*

MAP is a food preservation method that alters the composition of gases within the packaging by reducing O₂ levels and increasing CO₂ concentrations. This modification slows down the overall metabolic activities of the packaged produce, thereby extending its shelf life. MAP is an economical method for maintaining the freshness of fruits and vegetables during prolonged storage. Petroleum-derived films used in MAP have shown effectiveness in extending the shelf life of various agricultural products [126, 127]. By keeping relative humidity levels at 90–95%, MAP prevents water loss, which helps avoid fruit shriveling, delays ripening, and reduces respiration rates [128]. Packaging materials made from biodegradable substances offer environmentally friendly alternatives to traditional PET and HDPE plastics [129]. Scientific studies demonstrate that incorporating oxygen absorbers into bio-based packaging can significantly prolong the freshness of strawberries [77]. Biodegradable laminates have shown effective performance when used in MAP for vegetables. These materials serve a dual purpose; they extend the shelf life of berries while safeguarding them from harmful environmental pollutants and disease-causing microorganisms [130].

5.3 *Nanocomposite Packaging*

Biopolymer nanocomposites have established themselves as eco-friendly and functional alternatives to non-degradable polymers, which harm the environment by restricting soil oxygen flow and reducing land fertility. The food industry now uses biopolymeric composites that combine two or more biopolymers with optional additives and natural fibers (NFs) [107]. The combination of these materials demonstrates superior biodegradation performance, and their packaging capabilities have been widely investigated by researchers. The incorporation of traditional nanoparticles (NPs) or nanofillers enhances the tensile strength, permeability, and moisture barrier properties of pure biopolymer films, which often exhibit limited barrier and mechanical performance. These improvements result from the increased surface area between NPs and the biopolymer matrix, as well as their strong bonding interactions [131, 132]. The production of nanocomposite films involves standard processes such as electrospinning, molding, layering, and micro- or nano-encapsulation methods. The most effective nanoparticles in food packaging applications are polysaccharide-based

nanoparticles, like starch, alginate, chitin, and chitosan. Starch-based nanocrystals improve moisture resistance and material strength, while alginate-based NPs exhibit exceptional resistance to chemical damage and temperature fluctuations. Nanoparticles made from chitin and chitosan offer excellent food packaging capabilities due to their affordability, biodegradability, biocompatibility, and antibacterial characteristics [133, 134]. The optimal properties of these nanocomposites depend on NP dimensions, morphology, surface area, and aspect ratio, with proper dispersion and orientation of NPs within the polymer matrix being a critical factor [135, 136]. Biopolymer nanocomposites offer a sustainable approach to reducing the environmental impact of packaging materials. By preserving food quality throughout storage and distribution, they provide an environmentally friendly alternative to traditional packaging methods [137, 138].

5.4 Active Packaging

Active packaging systems employ advanced technological approaches that incorporate interactive components designed to actively engage with the food materials and their corresponding packaging environment. These interactions are specifically aimed at enhancing food preservation by safeguarding quality, ensuring food safety, and prolonging the freshness of packaged foods [139, 140]. Active packaging works through a protective shielding mechanism which blocks outside factors and through environmental regulation inside the packaging, thus delivering efficient food preservation. The two primary systems of active packaging include releasing mechanisms, with CO₂ emitters, and absorbing mechanisms, which consist of oxygen absorbers, CO₂ scavengers, ethylene removers, and humidity controllers [141]. The ability to release and absorb substances allows intelligent and active packaging systems to resolve multiple preservation issues that affect food manufacturers [139].

5.4.1 Oxygen Absorbers

Food products show high sensitivity to oxygen exposure because this exposure initiates oxidation reactions and contributes to microbial spoilage. These processes create an environment where nutrients disappear, along with color changes and vitamin breakdown, ultimately shortening product longevity [139, 142]. Effective storage management of packaging requires oxygen absorbers to block oxygen permeation while sustaining a controlled atmospheric environment. Active packaging systems benefit from oxygen absorbers because they improve packaging barriers and protect against rancidity and deterioration while controlling excess oxygen content. The four types of oxygen absorbers include metallic scavengers (iron powder, ferrous oxide), natural absorbers (ascorbic acid, lignin, catechol), inorganic scavengers (sulfite, titanium dioxide), and enzymes [143, 144]. Food packaging absorbers exist in different

formats, including sachets, pads, films, cards, and labels, which serve the purpose of decreasing or eliminating food product oxygen residuals [145, 146].

5.4.2 Carbon Dioxide Absorbers

The use of carbon dioxide absorbers enables effective microbial control of bacteria, yeast, and mold, alongside their function of removing excess carbon dioxide to prevent package bursting. Carbon dioxide absorbers exist in two forms: (a) chemical-based absorbers, which include calcium hydroxide, potassium hydroxide, sodium hydroxide, calcium oxide, and sodium carbonate [147, 148], and (b) mechanical absorbers, consisting of silica gel, zeolite, and activated carbon [149]. Managing carbon dioxide levels through these materials enables better product quality and lowers the environmental impact [150].

5.4.3 Ethylene Absorbers

Food products experience faster ripening and decreased storage time because ethylene concentrations in any amount elevate respiration rates during storage, which leads to reduced product shelf life [151]. The utilization of ethylene absorbers allows operators to chemically and physically eliminate ethylene inside sealed storage areas. The three main categories of ethylene absorbers consist of metals and metal oxides, silicates and zeolites (including clays and vermiculite), and nano-carbon structures [152, 153]. The most common ethylene absorber is potassium permanganate (KMnO_4), which functions independently and also within nanosilicates, nanoclays, and nanozeolites. When KMnO_4 comes into contact with oxygen, it produces water and carbon dioxide, which effectively slows down the ripening process [154].

5.4.4 Moisture Absorbers

Sealed packaging that contains excessive moisture or water vapor enables microbial growth while reducing transparency and changing texture, which shortens food product shelf life. Moisture absorbers regulate package humidity so food maintains its sensory characteristics and achieves longer shelf life. The absorption materials used for moisture control contain hygroscopic elements, which include silica gel, MMT or bentonite clays, and calcium oxide [155]. Food manufacturers use pads, sachets, and films to incorporate moisture barriers from these materials, which protect dry food products [156].

5.4.5 Carbon Dioxide Emitters

The carbon dioxide emitter systems create food packaging environments with precise CO₂ levels, which preserve taste and scent qualities while reducing package volume and controlling microbial growth to increase product longevity. The packaging systems incorporate functional materials like ferrous carbonate, sodium bicarbonate, ascorbic acid, and citric acid, which are integrated within sachets or pads [157]. Scientific data indicate that precise CO₂ emitter application allows for adequate CO₂ distribution, which improves the physicochemical nature of packaged food items. Higher CO₂ levels provide maximum benefits to meat and poultry products by both suppressing bacteria growth and reducing product loss [158].

5.5 Antimicrobial Packaging

Active packaging systems have received substantial research focus in recent years for their role in developing methods to stop microbial growth through antimicrobial food packaging techniques. Packaging materials embedded with antimicrobial agents establish a controlled environment inside packages, which extends microbial growth inhibition, delays the microbial growth process, or minimizes microbial growth [117]. These packaging systems help minimize food waste by preserving quality as well as maintaining an attractive appearance while prolonging the freshness of packaged foods [159]. Microbe-inhibiting compounds are categorized into multiple groups, including: (a) natural substances, like organic acids, enzymes, and polymers; (b) inorganic materials, like metals and metal oxides; (c) essential oils, including thyme, pimento, oregano, citron, clove, lemon balm, lemon verbena, and cypress leaf oils; (d) herbal extracts, like those from green tea, grape seed, bearberry, rosemary, ginger, garlic, and sage; (e) pure bioactive compounds, like thymol, carvacrol, and caffeic phenethyl ester (CPAE); and (f) peptides, like nisin and lactoferrin [160, 161]. The food industry utilizes bio-nanocomposites extensively by incorporating metal nanoparticles (silver, copper, zinc) and metal oxide nanoparticles (zinc oxide, titanium dioxide, copper oxide) alongside chitosan biopolymers to obtain antimicrobial effects [162]. Research demonstrates that films made from chitosan demonstrate important antimicrobial characteristics that both restrict microbial proliferation and lengthen the storage duration of packaged foods, thus making them potential materials for antimicrobial packaging applications [163]. Chitosan-based film effectiveness depends on various factors, including concentration level and molecular weight, as well as added substances, microbial species, and environmental temperature. The antimicrobial effectiveness of composite films increases when chitosan receives nanoparticle integration. Scientific studies have found that adding clove essential oil to zinc oxide-reinforced gelatin films successfully delays microorganisms in shrimp packaging and enhances food safety while extending shelf life [164]. CPAE nanoparticles function as phenolic compounds that successfully suppress microbial development in cellulose-based packaging films [165].

5.6 *Antioxidant Packaging*

Both lipid oxidation and microbial growth act as major agents that negatively affect food quality and reduce the shelf life of products. The food sector requires effective prevention of oxidation because it results in lipid decomposition, texture modification, off-tastes, and color changes [165, 166]. BHT and BHA, together with TBHQ, represent common synthetic antioxidants that food manufacturers traditionally use to suppress oxidation processes [167]. The exploration of natural alternatives has become necessary because of health-related concerns. The list of natural antioxidants consists of (a) phenolic compounds, (b) flavonoids; (c) plant extracts and (d) essential oils (169). Research has shown that antioxidant characteristics emerge when curcumin and ascorbyl dipalmitate (ADD) nanoparticles are combined with cellulose films, while tea polyphenol and chitosan nanoparticles produce antioxidant properties in gelatin films [159]. The addition of UV absorbers, such as benzotriazoles, benzophenones, titanium dioxide, and zinc oxide, to packaging materials blocks UV radiation, thus protecting light-sensitive foods, including oils and beverages, from photo-oxidation. These additives contribute to preserving nutritional value, product quality, and the safety of packaged foods through their light-controlling properties [159].

5.7 *Intelligent Packaging*

Packaged product deterioration depends on two fundamental factors: (a) food properties, including pH, water activity, redox potential, respiration rate, and antimicrobial compounds, together with microbial presence, and (b) external conditions. For example, moisture levels, preservation temperature, and gas composition in the package headspace [168, 169]. Intelligent packaging presents an innovative approach for detecting internal package issues, which adds value to products through quality protection, market sustainability, and safety assurance. The technology comprises spoilage indicators and time-temperature indicators (TTIs) to deliver real-time freshness and safety data through sensing, recording, tracing, and communication features [170].

6 *Safety Challenges in Modern Food Packaging*

The growing accumulation of plastic waste causes major environmental issues, adding to waste, climate impact, and carbon dioxide production. Additionally, chemical substances from plastic packaging may transfer into food, creating hazards to human health. Despite this, the safety of packaging materials frequently receives little attention. A particular concern is the use of nanosized additives in packaging,

as these particles may leach into food, especially under prolonged contact or at elevated storage temperatures. Health risks from nano-packaging materials arise through three pathways: skin contact, inhalation, and ingestion. These risks rely on elements like the migration degree of nanomaterials into food, their toxicity, particle size, and the frequency of consumption [171]. Furthermore, the degradation of bio-nanocomposites can release nanoparticles into ecosystems, potentially causing environmental harm. Modern packaging technologies, including active, antimicrobial, antioxidant, and intelligent packaging, require direct food contact, necessitating strict safety regulations. To ensure safety, nanomaterials used in packaging must undergo rigorous testing, including migration, cytotoxicity, and eco-toxicity assessments [172]. Recently, biodegradable polymers, or biopolymers, have gained attention as eco-friendly replacements for conventional plastics. Produced from sustainable materials including starch, cellulose, or proteins, biopolymers offer lower toxicity and reduced environmental impact. However, their safety must be carefully evaluated, as additives or processing aids may migrate into food [14]. High-tech analysis tools, including mass spectrometry and chromatography, are used to detect and quantify such migration [173]. LCAs are also critical for assessing the ecological footprint of biopolymer-based packaging, ensuring alignment with global sustainability goals [174].

7 Future Challenges and Opportunities

Biopolymers are emerging as sustainable alternatives for food packaging, offering environmental benefits over conventional plastics. The widespread adoption of biopolymers remains restricted due to their weak structural properties, thermal instability, barrier deficiencies, high prices, and insufficient knowledge about biodegradation processes [175, 176]. The combination of nanotechnology and nanobiocomposites offers potential enhancements to biopolymer functionality, enabling packaging products with antimicrobial protection while offering oxygen-resistant functions [177]. Time-sensitive food quality assessment is possible with smart packaging technology, which incorporates biosensors [178]. Business applications of self-healing and self-cleaning bioplastics remain under development because researchers must study their durability while finding ways to reduce costs and improve commercial potential [179]. The main difficulties in biodegradable materials stem from toxic substance emissions during breakdown, inadequate resistance to water, and insufficient recycling methods [174]. Researchers must conduct studies to improve storage conditions for packaging materials while developing antiviral and antimicrobial coatings and investigating gas permeability [180]. The cytotoxic effects of nanofillers in biocomposites must be evaluated, with a focus on controlled release mechanisms and minimizing nanoparticle contact with food [92]. The commercialization of smart packaging technologies demands better performance in terms of sensitivity and specificity. The main impediments to commercial success include legislative hurdles, high costs, and requirements for public education and academic-industry partnerships.

Research should focus on developing eco-friendly biopolymer-based food quality trademarks and packaging solutions that show promising potential [175, 178].

8 Conclusion

Research in food packaging is advancing constantly because of both changing life patterns and rising environmental sustainability concerns. Academic scholars now dedicate more effort to developing biopolymer-based materials that serve as sustainable food packaging alternatives. The widespread adoption of biopolymers remains limited because of technical obstacles that occur during processing and practical application. This review provides essential knowledge to food packaging researchers who need to overcome these barriers to biopolymer system development. Scientists have developed different methods to boost biopolymer-based material performance through the addition of plasticizers, the creation of biopolymer mixtures, and the integration of nanomaterials. Research indicates that nanomaterials specifically demonstrate strong potential to enhance the key characteristics of bio-nanocomposites, including efficient permeability, superior mechanical properties, and antimicrobial resistance, which lead to new industrial applications. Furthermore, research shows that sustainable, biodegradable, and renewable polymers, along with bio-nanocomposites, possess great potential for transforming food preservation methods. The food packaging industry will discover sustainable development opportunities alongside enhanced food safety when it adopts new, creative materials and technologies.

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Chapter 15

Patents, Regulatory Issues, and Future Prospects of Biopolymers

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Abstract Presently, the significant advancements in biopolymer research have accelerated the push to replace traditional petroleum-based polymers with sustainable alternatives. These biopolymers have found several applications including encapsulation, regenerative medicine and cosmetic formulations. Consequently, the advancements highlight the transformative potential of these sustainable polymers across various industries. In pursuance of this goal, patents and regulatory frameworks are the next hurdles needed to be considered. These systems play crucial roles in shaping the development and commercialization of biopolymers in today's market. While patents provide intellectual property and serve as a repository of technical knowledge on novel processes and applications in the field, Regulatory Standards on the other hand ensure the safety, efficacy, and environmental sustainability of biopolymer products. This could influence their market viability and acceptance, which could guide biopolymer innovation, influencing both commercialization and future applications. Therefore, understanding the relationship between patents and regulations is important for navigating issues and exploring the full potential of biopolymers in addressing global sustainability challenges. This chapter seeks to explore the patents and regulatory frameworks that guide the biopolymer industry spanning from its introduction to its current and future outlook.

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1 Introduction

Increasing concerns on plastic pollution complexed with climate change and resource depletion has sparked interest in sustainable innovations which include the development of biopolymers. Biopolymers encompass polymers produced using living organisms ranging from microbes and algae to plants and animals [1]. Similar to other polymers, biopolymers are essentially large macromolecules made up of numerous repeating units [2]. The growing interest in biopolymer-based materials stems from the urgent need to transition away from petroleum-derived polymers and monomers, which are finite and environmentally detrimental. Therefore, embracing biopolymer developments presents a sustainable alternative, offering industries renewable and biodegradable materials that are environmentally friendly and safe [1].

Moreover, biopolymers offer several advantages including biodegradability, compostability, and reduced carbon footprint, making them an attractive alternative for various applications in the packaging, agriculture, healthcare, and textiles industries [3]. Based on their origin and synthesis, Biopolymers are broadly categorized into three main groups including natural biopolymers, which occur naturally in biological systems, such as cellulose, starch, chitosan, and alginate [4], microbially derived biopolymers, synthesized by microorganisms, including polyhydroxyalkanoates (PHAs) and bacterial cellulose and Biobased polymers produced using renewable monomers, such as polylactic acid (PLA), biobased polyethylene (Bio-PE), and biopolyethylene terephthalate (Bio-PET) [5]. Consequently, the term “biopolymers” encompass both natural polymers, which are those occurring naturally derived (such as cellulose or starch), and biobased polymers, synthesized using natural monomers [5].

In the food industry, biopolymers are utilized in edible coatings, emulsions, and packaging materials. Meanwhile, they find other applications in drug carrier systems, medical prosthetics, wound dressing materials, and tissue scaffolds in the health industry. Many studies have confirmed their non-toxicity and biocompatibility hence their myriad applications, even in the pharmaceutical industries. This stems from their monomeric units which include amino acids, sugars and nucleotides which are safe to biological systems [6].

While biopolymers have the potential to mitigate plastic waste and dependency on fossil fuels, their commercialization and widespread adoption face several challenges, particularly in terms of their intellectual property (IP), regulatory compliance, and market scalability. As companies and research institutions invest in novel biopolymer formulations and processing techniques, these patents provide a legal framework to protect their technological advancements and incentivize further research. Meanwhile, regulatory systems are also necessary to ensure the safety and guidance of the biopolymer industry to prevent possible dangers in the future [7].

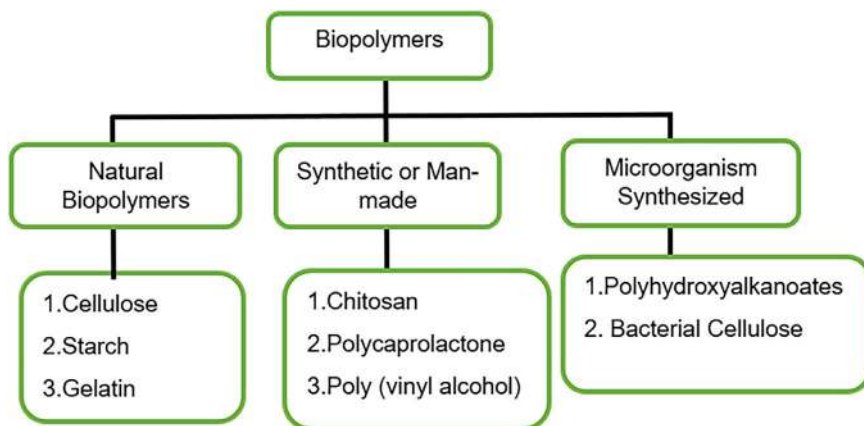


Fig. 1 Classification of biopolymers based on synthesis (Adapted from [8])

This chapter seeks to explore the progress made in biopolymer patents and their regulatory frameworks. It will span from their historical perspective to future outlook (Fig. 1).

2 Contrast between Conventional Polymers and Biopolymers

Polymers are essential materials used across various industries, ranging from packaging to biomedical applications. Traditionally, most polymers are petroleum-based (conventional polymers), offering durability, cost efficiency, and versatility. However, the environmental concerns associated with their non-biodegradability and carbon footprint have led to increased interest in biopolymers, which are produced from renewable sources and are often biodegradable. This section explores the fundamental differences between conventional polymers and biopolymers, considering aspects such as source materials, mechanical properties, environmental impact, applications, and cost.

Conventional polymers are synthesized from petrochemical sources, primarily derived from crude oil and natural gas. The most commonly used conventional polymers include; polyethylene, polypropylene, and polystyrene. Since these materials originate from finite fossil fuel resources, their production is energy-intensive and contributes significantly to greenhouse gas emissions [9]. Conventional plastics are cheaper to produce due to well-established infrastructure and large-scale production capabilities. The cost of conventional polymers is driven by oil prices and refining efficiency, making them economically viable for mass production. One of the major demerits of conventional polymers is their long degradation time. Plastics like PE and PP can stay in the environment for several years, leading to significant issues such

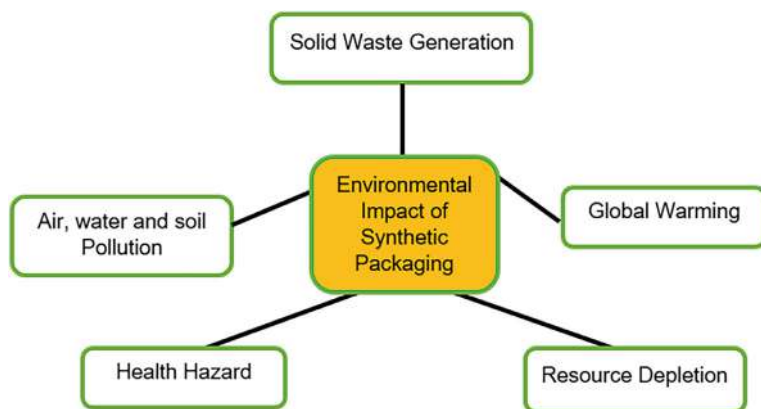


Fig. 2 Environmental impact of synthetic packaging materials

as microplastic accumulation in marine and terrestrial ecosystems, landfill overflow due to non-biodegradable plastic waste, and chemical leaching of additives, potentially harming wildlife and human health. Generally, these challenges of synthetic conventional polymers may have lasting implications on the environment (Fig. 2).

On the other hand, biopolymers are produced from renewable sources, including plants, algae, and microorganisms. Considering the wider range of sources, biopolymers are quite numerous with some widely studied biopolymers including; polylactic acid (from corn starch or sugar cane), polyhydroxyalkanoates (from bacteria-synthesized organic substrates), starch-based polymers (from potatoes, corn, wheat), and chitosan (crustacean exoskeleton). Since biopolymers utilize renewable biomass, their production generally results in lower carbon emissions and helps reduce reliance on fossil fuels [10]. Many biopolymers offer biodegradability, meaning they can be broken down by microorganisms into carbon dioxide, water, and biomass under appropriate conditions. For instance, polylactic acid biodegrades in industrial composting facilities, although it may require high temperatures. With chitosan, due to its' water solubility, it degrades easily without the production of harmful residues. It is however worth noting that biodegradability depends on environmental conditions, such as temperature, humidity, and microbial activity [11].

3 Patents in Biopolymer Technology

As global demand for sustainable materials increases, companies and researchers are investing heavily in the development of novel biopolymer formulations, enhanced biodegradability mechanisms, and efficient production processes. Accordingly, Patents do not only provide a competitive advantage but also encourage collaboration

through licensing agreements, enabling broader adoption of biopolymer technologies [12].

The first patent application, which was on biopolymer-based hydrogels, was filed in 1935 and then granted in 1936 [13]. From 2015 to 2020, patent applications for biopolymer-based hydrogels rose from 5,331 to 8,910, with the highest filing activity observed in the United States, Europe, China, and Japan [14]. Over this period, more than 1,000 organizations worldwide encompassing universities, academic institutions, companies, foundations, and governing bodies became involved in patent activities related to biopolymer-based hydrogels [13].

The International Patent Classification (IPC) is a hierarchical system in the form of codes, which divides all technology areas into a range of sections, classes, subclasses, groups, and subgroups. By 2020, a total of 11,895 patent documents related to biopolymer-based hydrogels were identified. In contrast to 1995, when only 51 patent documents were registered (25 applications and 26 granted patents), the year 2020 saw a significant increase with 934 documents (698 applications and 236 granted patents). Notably, the year with the highest number of granted patents was 2017, with a total of 254 [13]. From 1915 to May 2023, 44,983 patent applications were found with 1958 patents approved on hydrogels [1].

Patents are good indicators of the rate of invention, which is an important factor in innovation [15]. The patent landscape for hydrogel-based bioinks in 3D bioprinting shows substantial growth, with 173 patents published from 2013 to 2024, particularly increasing from 2018 onward, indicating heightened interest and innovation in biopolymer applications for healthcare and regenerative medicine [16]. Nanocellulose patent filings in pharmaceuticals reveal a total of 215 patents from 2011 to 2023, with significant applications in design and manufacturing, drug delivery, wound healing, and tissue engineering, highlighting its growing industrial relevance [17]. Between 1996 and 2022, 288 biopolymer patent documents were filed, with notable increases in 2007, 2013, and 2021, and a peak of 21 in 2022.

Globally, the United States led with 84 patents, indicating growing innovation in this field [13]. Patent filings for biodegradable polymers showed a constant increase, particularly for polycaprolactone (PCL) since 2005, while poly (lactic acid) (PLA) and poly (butylene adipate-co-terephthalate) (PBAT) have reached maturity, indicating a shift toward market-oriented research and development opportunities [18]. Notably, for approximately 240 biopolymer applications, there is only one application related to waste treatment. While most patents remain pending, a decline in filings was observed during the 2010–2012 global recession period. However, subsequent surge in commercial activities highlights the increasing interest in biopolymer development, as reflected in the growing number of patents in recent years. As companies and researchers continue to innovate, the focus on creating sustainable solutions is becoming increasingly prominent.

4 Inventions Covered

Increasing commercialization of biopolymer-based hydrogels is evident in sectors of healthcare to the food industry. This trend is elucidated in biopolymer-based hydrogels due to their biocompatibility and biodegradability, making them promising for applications requiring controlled interactions with biological systems [19].

Through its development, hydrogels have been researched on their use in drug delivery systems, tissue engineering, wound healing, regenerative medicine, and food preservation [20]. In drug delivery, they are specifically designed to release drugs in a controlled manner, optimizing therapeutic efficacy while reducing side effects [21]. By encapsulating drugs, hydrogels facilitate sustained or targeted release over time, leveraging stimuli-responsive mechanisms like pH sensitivity to enhance precision and effectiveness.

In tissue engineering, biopolymer-based hydrogels serve as scaffolds that support the growth of new tissues by providing a 3D structure similar to the extracellular matrix. In addition, the hydrogel polymer creates a suitable environment for healing from infections further showcasing the potential of these polymers in wound care and regenerative medicine. Correspondingly, some studies have used hydrogels alongside stem cells to facilitate tissue repair and regeneration. They play a role in integrating cell therapies into damaged tissues or organs [22]. Finally, biopolymers have also been investigated for potential use in food packaging to preserve freshness by acting as barriers against moisture and gases.

5 Biobased Polymers and Their Applications

Starch is a naturally derived biopolymer that exists in granules and serves as the result of photosynthesis in plants. It is a carbohydrate-based polymer that is widely sourced from crops like wheat, rice, corn, and potatoes [23]. Composed primarily of linear polysaccharides, starch has extensive applications in both food-related and non-food industries. Thermoplastic starch (TPS) polymers, known for their versatility, are commonly utilized to produce films for packaging, including items like shopping bags, bread bags, fishing bait bags, sanitary product wraps, packing materials, and mulch films. Looking ahead, TPS could be employed in foam loose-fill packaging and injection-molded products, such as food take-out containers. Additionally, modified starches have proven adaptable, finding applications across a variety of sectors [1].

Cellulose is the primary component of plant cell walls, characterized by its complex polysaccharide structure and crystalline morphology. It is a robust polymer with notable mechanical properties, featuring a tensile strength ranging from 62 to 500 MPa and an elongation of approximately 4%. While chemically pure cellulose can be produced using specific bacteria, the process faces significant challenges due to low yields and high costs. These limitations hinder its widespread adoption for large-scale industrial applications [24].

Chitin and chitosan are among the most abundant natural amino polysaccharides, derived primarily from the shells of crustaceans like prawns and crabs. These valuable biobased polymers are commercially produced through chemical extraction processes using waste materials from crabs, shrimp, and prawns [23]. Chitosan exhibits several desirable properties: it is biodegradable, biocompatible, chemically inert, has high mechanical strength, forms films well, and is relatively inexpensive [25].

Pullulan is a linear, water-soluble polysaccharide primarily composed of maltotriose units linked by α -1,6 glycosidic bonds. First identified by Bauer in 1938, pullulan is widely utilized in the food industry due to its tasteless and odorless nature. It serves as a low-calorie food additive, providing bulk and texture while being slowly digested by the body. This makes it an ideal component for enhancing food products without adding significant calories or flavor.

Collagen is a highly valuable biomaterial due to its biocompatibility, biodegradability, and low antigenicity. One of its primary applications in ophthalmology involves the use of collagen films as drug delivery systems, which facilitate the slow release of incorporated drugs [26]. Additionally, collagen plays a significant role in tissue engineering by serving as a material for skin replacement, bone substitutes, and the creation of artificial blood vessels and valves [27].

Alginate is a linear polysaccharide that is naturally abundant, synthesized by both brown seaweed and certain soil bacteria [28]. Sodium alginate is the most commonly utilized form in industries due to its derivation from algal purification processes [29]. Alginates serve multiple roles as viscosifiers, stabilizers, and agents for forming gels, films, or binding water across various sectors [11]. Their applications are particularly prominent in pharmaceuticals and food products where they function as effective gelling agents.

When patents for nanocellulose were studied [17], classified them based on functionality of the nanocellulose. Mainly into five classes: design & manufacturing, cell culture & cell technology, tissue engineering, wound healing, and drug delivery. Lignocellulosic biomass was used for the production of crystalline cellulose (nanocellulose) in one of the patents studied; U.S. Patent N° 2016/0184438 A1, [30], is categorized within design and manufacturing. Similarly, another patent described the application of nanocellulose particles to create water-repellent membranes and films through the use of superhydrophobic surfaces [31]. This process involves hydrophilization achieved by incorporating nanocellulose particles alongside a modifier compound, thereby linking the patent to both design and manufacturing functionalities. In the realm of cell culture systems and technologies, patent EP 3,750,982 A1 [17] introduced a cell culture plate enhanced with nanofibrillar cellulose, used as a barrier to divide the plate into at least two distinct compartments. Within the wound healing category, the patent WO 2018/130390 A1 focused on a system that loads a hydrophilic, naturally derived three-dimensional network, formed from cellulose nanofibers, with lipid-based dermal carrier systems [17].

6 Applications Across Industries

Biopolymers are increasingly recognized for their industrial applications, particularly as sustainable alternatives to conventional synthetic polymers. Their versatility spans various sectors, including packaging, agriculture, and environmental engineering, where they contribute to reducing ecological footprints and enhancing biodegradability. Biopolymers have been employed in various medical fields, such as surgery, orthopedics, and dentistry, to support healing, repair damaged tissues, or restore lost bodily functions. Their applications include drug delivery systems, implants, devices, prostheses, and diagnostic tools. Some biopolymers contribute to the formation of connective tissues and assist in tissue functionality, like human cartilage, while others act as signaling molecules to activate the endocrine system. Thanks to their natural origins and exceptional biochemical, mechanical, and thermal characteristics, biopolymers are highly suitable for a wide range of pharmaceutical and biomedical uses [1]. Chitosan enhances muco-adhesion and permeability, making it suitable for oral and nasal drug delivery [32]. Alginates have also been found to form hydrogel matrices that provide controlled drug release, making them suitable for wound dressing and gastrointestinal drug formulations.

Biopolymers like PLA (polylactic acid) and PHA (polyhydroxyalkanoates) are utilized in food packaging, offering advantages such as reduced carbon footprints and enhanced biodegradability compared to traditional plastics. PHA for instance, is very flexible, tough and has excellent barrier properties that make it a good prospect for manufacturing biodegradable trays, containers, and packages for frozen foods [33], while PLA is transparent, has heat resistant properties, and a good oxygen barrier, making it ideal for making disposable containers, flexible packaging and cutlery [34]. Life cycle assessments reveal that biopolymer-based packaging offers a promising solution to mitigate pollution and enhance soil health, tackling the environmental issues associated with traditional plastics [35]. Meanwhile, milk-derived biopolymers can be used in producing complex food products as a result of the rigid oil-in-water structure and emulsion-forming properties.

Proteins from milk, eggs, and fish and polysaccharides such as xanthan gum, modified cellulose, and starches act as beneficial emulsions, due to their ability to adhere and their functional properties that produce greater surface charge, pressure, adsorption kinetics, droplet stability, and affinity, which facilitates marketing. Of products with a slogan of being “consumer friendly” [36]. When modified starch and whey proteins were employed as biopolymers for emulsions of rice bran oil, lipid oxidation stability was greatly improved. This makes it a viable way for application in the commercialization of foods with liquid phases in the foreseeable future [37].

Biopolymers are utilized in the agricultural sector as biodegradable films for mulching and also serve as fertilizers that release nutrients gradually and as well enhance soil stability and nutrient retention. As indicated by [38], the antimicrobial properties of biopolymers make them ideal for crop protection and as additives in agricultural products, reducing the impact of synthetic fertilizers and plastic pollution.

Biopolymers are derived from renewable biomass sources, for instance starch, cellulose and microbial fermentation which have been utilized in agricultural applications. They are used in biodegradable mulch films, controlled-release fertilizers, soil conditioners, and plant growth stimulants [10]. The biodegradability, non-toxic nature, and compatibility with soil microbiota nature of biopolymers make them feasible and better alternatives to petroleum-based plastics and chemicals in farming. Meanwhile, mulch films are widely used in agriculture to conserve soil moisture, regulate temperature, control weeds, and improve crop yield. While polyethylene (PE)-based mulch films have been used, their accumulation in soil contributes to microplastic pollution and soil contamination [39]. Biopolymer-based mulch films offer a sustainable alternative to these polyethylene-based mulch films by degrading into natural components, reducing environmental impact and disposal costs. PLA-based mulch films according to [40] enhance soil microbial activity while improving weed suppression and soil moisture retention.

7 Breakthroughs in Biopolymer Research

Current developments in biotechnology and material science are advancing biopolymer innovation, ensuring progress in sustainability and industrial applications. Techniques like precision fermentation and genetic engineering facilitate the production of high-performance biopolymers. The optimization of microbial strains such as *Escherichia coli* and *Cupriavidus necator* using CRISPR-Cas 9, which boosted yields of polyhydroxyalkanoates (PHA) and polylactic acid (PLA) through refined metabolic pathways [8, 41]. Engineered PLA copolymers show improved durability and heat resistance, widening their industrial applications [42].

Furthermore, enzyme-catalyzed polymerization, where enzymes like lipases are used to produce polymers under controlled conditions. It presents an energy-efficient and non-toxic approach which aligns with circular economic objectives [43]. On the other hand, self-healing biopolymers with embedded microcapsules similar to biological repair mechanisms lead to prolonged material lifespans in several applications including medical devices [44].

Biopolymers are utilized in smart packaging devices as they possess responsive properties to environmental facts such as pH, temperature, and moisture. They also find applications in delivery systems which enable targeted drug delivery systems that activate under specific biological conditions [27].

Meanwhile, artificial intelligence and machine learning techniques are transforming biopolymer development by streamlining material innovation and production processes. These technologies enable the rapid virtual testing and development of new formulations and precise optimization of manufacturing conditions. Predictive algorithms also help forecast material behavior under different scenarios, hastening the creation of eco-friendly, high-performance biopolymers [45].

Transformative growth is expected in the biopolymer industry via several key developments. Advancements in genetic engineering and computing would enable

custom-designed biopolymer structures. Furthermore, the integration of nanotechnology would improve the material properties including tensile strength and barrier properties. Other advantages lie in self-repairing biopolymers and closed-loop recycling systems which would address the end-of-life challenges.

These advancements elucidate the remarkable multi-disciplinary collaboration among biologists, material scientists, and data scientists which is set to lead to more biopolymer innovations, which could provide feasible and yet sustainable solutions to currently faced plastic-derived challenges.

8 Regulatory Landscape

The rise in the use of biopolymers has led to the establishment of regulatory guidelines for their production, utilization, and disposal. These guidelines differ, affecting how biopolymer-based products are brought to the market and used. The guidelines ensure that biopolymers meet standards, such as being biodegradable, compostable, safe for use with food, and having a minimal impact on the environment.

In the United States of America, biopolymer regulations fall under multiple agencies (Table 1):

Table 1 Summary functions of patent regulatory organizations in various countries/continents

Country/Continent	Organization/Body	Function summaries
USA	FDA	Regulates biopolymers used in food packaging Ensures the safety of materials for food contact applications
	EPA	Overseas environmental impact of biopolymers
Europe	ASTM international European union	Developed standards for biodegradability and compostability Restricts some single-use plastics promoting biopolymer alternatives Give criteria for industrial compostability Ensure chemicals used for biopolymer production are environmentally friendly Focused on reducing plastic pollution
Asia	Ministry of ecology & environment (China) Japan bioplastics association (Japan) Central pollution control board (India)	Plastic waste reduction; encouraging biodegradable plastics Ensure compostability and renewability requirement is met Encourages use of compostable plastics

- Food and Drug Administration (FDA): Regulates biopolymers used in food packaging under **Title 21 of the Code of Federal Regulations (CFR)**, ensuring materials meet safety requirements for food contact applications [46].
- Environmental Protection Agency (EPA): Oversees the environmental impact of biopolymers, including waste management policies and life-cycle assessment regulations.
- ASTM International: Develops standards for biodegradability and compostability, such as:

ASTM D6400: Specification for compostable plastics in municipal and industrial composting facilities.

ASTM D6866: Standard test for biobased content determination.

9 European Union (EU Directives and EN Standards)

The European Union has one of the most comprehensive regulatory frameworks for biopolymers, emphasizing environmental sustainability:

- EU Directive 2019/904 (“Single-Use Plastics Directive”): Restricts certain single-use plastics and promotes biopolymer-based alternatives [47].
- EN 13,432: Defines criteria for industrial compostability, requiring materials to biodegrade under specific conditions within six months [48].
- REACH (Registration, Evaluation, Authorization, and Restriction of Chemicals): Ensures that chemicals used in biopolymer production are non-toxic and environmentally safe [49].
- EU Green Deal & Circular Economy Action Plan: Promotes the use of sustainable biopolymers to reduce plastic pollution and achieve carbon neutrality.

10 Asia (China, Japan, India)

- China: In 2020, China introduced plastic waste reduction policies that promote biodegradable plastics and set quality standards for compostable materials [50].
- Japan: Implements the Biomass Plastic Label certification, ensuring that biopolymers meet compostability and renewable content requirements [51].
- India: The Plastic Waste Management Rules (2021) encourage the use of compostable plastics and mandate certification from the Central Pollution Control Board [52].

Apart from country-specific regulations, several international standards define the biodegradability and compostability of biopolymers. A few of these are listed below;

- ISO 17088: International standard for compostable plastics.

- TÜV Austria OK Compost & OK Biodegradable: European certification for industrial and home composting.
- BPI (Biodegradable Products Institute) Certification: Recognized in North America for verifying compostability in controlled conditions.

These certifications help manufacturers and consumers identify sustainable biopolymer products that meet regulatory requirements.

11 Challenges in Regulatory Compliance

The regulation of biopolymers is complex, as it involves multiple agencies, standards, and certifications across different regions. While regulations aim to promote sustainability, manufacturers, policymakers, and consumers face several challenges in ensuring compliance, most of which can be classified as either technological, economic, or regulatory. Some of the challenges are more difficult to resolve, while others require a shift in perspective from all benefiting and contributing stakeholders in the biopolymer industry.

One of the primary challenges in biopolymer regulation is the inconsistency of standards across different regions. While several international standards exist, such as ASTM D6400 (USA), EN 13,432 (EU), and ISO 17088 (global), they have distinct criteria for biodegradability and compostability. For example: ASTM D6400 requires there be at least 90% biodegradation within 180 days in an industrial composting facility [53], while EN 13,432 also specifies similar criteria but includes additional disintegration tests, heavy metal content limits, and impact on compost quality [48], ISO 17088 provides a global framework but allows countries to modify requirements based on local waste management conditions [54]. These differences create challenges for biopolymer manufacturers who want to market their products globally [55]. Companies must often undergo multiple testing procedures to meet different regulatory standards, increasing costs, and delaying product launches [56].

Another challenge will be the high cost of testing and certification. Obtaining certification for compostable and biodegradable plastics involves rigorous testing under controlled conditions, which can be expensive. With testing for biodegradability, disintegration, and toxicity under ASTM or EN standards costing thousands of dollars per product batch, following these can put a strain on the industries and even individual scientists who develop novel biopolymer materials. Again, certifications like TÜV Austria's OK Compost or BPI (Biodegradable Products Institute) certification require periodic renewal, adding to long-term expenses. While large corporations can absorb certification costs, small and medium-sized enterprises (SMEs) often struggle with compliance due to limited resources. A study by the Ellen MacArthur Foundation (2021) found that cost barriers prevent many businesses from adopting certified compostable packaging, limiting the market penetration of biodegradable alternatives.

Despite certification efforts, consumer understanding of biopolymer labels remains a significant challenge. Terms like “biodegradable,” “compostable,” and “oxo-degradable” are often confused, leading to improper disposal practices. Many consumers assume “biodegradable” means the product will break down in any environment, including landfills. While EN 13432 also specifies similar criteria but includes additional disintegration tests, heavy metal content limits, and impact on compost quality [48]. Biopolymers like PLA (polylactic acid) resemble traditional plastics and often get mixed into recycling streams, causing issues in plastic recycling facilities [48]. Some manufacturers use vague or misleading claims about biodegradability, leading to regulatory scrutiny. Therefore, in response to these threats, authoritative bodies such as the Competition and Market Authority in the UK announced new guidelines in 2021 to prevent misleading environmental claims on plastic alternatives. Accordingly, public education and instructions on products on the use and disposal of these biopolymers could help solve these problems.

Another key drawback is the lack of the infrastructure needed to process compostable biopolymers. In light of the fact that materials even after meeting ASTM, D6400 standards may not degrade in the landfills and therefore require specific conditions to make it biodegradable. Therefore, unorganized recycling streams may cause increased pollution. As revealed by the U.S. Composting council, less than 15% of composting facilities accept biodegradable plastics. Again, packages labeled home compostable don’t meet the end goal as consumers lack the needed conditions to make the degradation possible [57].

Furthermore, these biopolymers end up in the general waste streams as many countries lack the separated waste collection systems for these biodegradable polymers. To solve this, countries including France and Italy have established waste sorting policies that ensure biodegradable plastics are included in organic waste to ensure they are processed in the right conditions.

Owing to the novel nature of biopolymers, there are several changes and evolution in several regulations. This goes a long way to impede commercialization strategies of new biopolymers which still make petroleum-based plastics heavily used despite its unsustainable nature [55]. But because biopolymers degrade into microplastics, regulatory bodies including the European Chemicals Agency continue to contemplate whether stricter guidelines are required [58]. Consequently, the decisions and regulatory frameworks may take some time to materialize and to guide the industry [59].

While biopolymer regulations promote environmental sustainability, challenges such as inconsistent standards, high certification costs, consumer confusion, and infrastructure limitations hinder widespread adoption. Future policies should focus on harmonizing international standards, investing in waste processing infrastructure, and improving consumer education to maximize the benefits of biodegradable and compostable bioplastics.

12 Future Regulatory Trends

One of the biggest challenges in the biopolymer industry is the lack of a unified global standard for biodegradability and compostability. Currently, different regions use separate certifications, such as ASTM D6400 (USA), EN 13,432 (EU), and ISO 17088 (global), leading to compliance difficulties for manufacturers. Efforts to align these standards will facilitate international trade in biopolymer products. Currently, the International Organization for Standardization (ISO) and the Organization for Economic Co-operation and Development (OECD) are actively working on developing more consistent global definitions and criteria for biodegradable and compostable plastics [60]. If successful, these efforts would reduce the burden of multiple certifications, simplify international trade, and ensure that consumers receive clear and consistent information about biopolymer products.

More countries are implementing Extended Producer Responsibility (EPR) policies requiring manufacturers to manage biopolymer waste. These policies are becoming a key regulatory tool to encourage manufacturers to take responsibility for the end-of-life management of their biopolymer products. The EU's Circular Economy Action Plan (CEAP) has already expanded EPR requirements to include bioplastics, ensuring that producers contribute to collection, recycling, or composting programs [61]. In North America, some states, such as California, Maine, and Oregon, have introduced EPR laws for plastics, which could eventually extend to compostable biopolymers. Canada is also developing a national EPR framework for plastic packaging [62]. These policies are expected to drive investment in composting and recycling infrastructure, ensuring that biopolymers achieve their intended environmental benefits.

Emerging policies may also address concerns about microplastic residues from biodegradable polymers. While biopolymers are often marketed as an environmentally friendly alternative to conventional plastics, some degrade into microplastics under certain conditions [63]. Consequently, stricter guidelines on biodegradable materials to ensure their safe production and utilization. To gain more understanding of them, the Environmental Protection Agency is actively involved in research to comprehend the mechanism and end products of biodegradation and its implications for the environment [64]. In addition, ISO 22403:2020 standard highlights the impact of microplastic pollution from bioplastics in water and land, which could shape future regulatory policies. Consequently, future guidelines and regulations would require new testing protocols to ensure biopolymers degrade fully into non-toxic by products in open environments.

There are significant changes in the regulatory frameworks as the governing bodies seek to find balance between innovation, environmental and consumer safety. Accordingly, regulations are expected to focus on standardizations to keep producers accountable while reducing microplastic pollution and enhancing consumer transparency. Governments are looking at setting up more composting facilities to enable proper degradation of these materials thus preventing environmental impact. As

scientific research and technological advancements proceed, regulatory frameworks will change accordingly to ensure they satisfy all needed prospects.

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