Complementary and Alternative Medicinal Approaches for Enhancing Immunity

Mehwish Iqbal

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Complementary and Alternative Medicinal Approaches for Enhancing Immunity

Ancient therapeutic systems have played a tremendous role in health preservation all around the globe for thousands of years; even the earliest humans on earth used these approaches along with simple surgical procedures for the betterment of their health. *Complementary and Alternative Medicinal Approaches for Enhancing Immunity* examines various aspects of health and diseases and the importance of basic but essential factors for the preservation of health and management of diseases.

Concisely written, the author discusses ancient ways to enhance self-healing abilities and stimulate the immune system, such as fasting, meditation, acupuncture, cupping therapy, balneotherapy and aromatherapy. The importance of nutrition and diet is also examined as it plays a crucial role in the prevention and causation of diseases.

Additional features include:

- Discusses how the integration of various CAM modalities helps in enhancing self-healing abilities and boosts the human immune system.
- Contains various topics from different systems of medicines that are taught widely as individual courses or discussed broadly at several institutes.
- Reviews Eastern pharmacotherapy and how using certain herbs, minerals and animal-based products aids in maintaining health and alleviating diseases.

Using evidence-based knowledge taken from ancient literature and recently published articles, this book will inform readers on the importance of holistic health approaches and some ancient treatment modalities that enhance the immune system to combat diseases.

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Whatsoever the author has learnt, it comes from her teachers and mentors; the book is therefore dedicated to them. Moreover, the author also devotes this book to all the health care professionals who have lost their lives in saving the lives of their patients during the recent COVID-19 pandemic (may their souls rest in peace).

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Preface

I developed an interest in natural medicines and holistic approaches in my childhood when my grandmother (late) used remedies to manage her family members. Although our ancestors had limited resources, they were healthier and more content with their lives than people of the current era. I always noticed how she was grinding herbs and spices in a traditional mortar and pestle made up of stone or *ammikallu* (grindstone) or making chicken's feet soup to manage cold symptoms or giving turmeric milk when there was any musculoskeletal pain. She might not have been aware of the scientific benefits of these remedies, but she gained that knowledge from her ancestors' wisdom about traditional healing. She could walk miles in her old age because she had good physical, mental and spiritual wellbeing. Every day, lots of people came to meet and greet her, and she was free from all the stress of this world since she had a calm and composed mind and could take decisions not merely for herself but for others. I always admired the life our grandparents were living, though at that time they lacked a lot of technological advancements for the household, for the luxury of humankind and for health care as well; still, they were close to nature. These people still had time to spend with their families, do some mild to moderate exercises, make fresh food for themselves, take proper sleep and meet with different people to enhance social interactions. They were using a variety of plant-based, animal-based and mineral products. These things always motivated me to adhere to nature and explore how people can benefit from following the principles of nature. I had a deep interest in that field since I always wanted to give my little contribution to this world by treating people with the traditional system of medicines, providing knowledge to them and counselling them about the benefits of holistic health and CAM approaches.

After commencing my clinical practice in Eastern medicine, I have noticed a pattern of diseases in people, among which a lot of ailments were related to lifestyle. This pattern exhibits how people are deviating from nature's principles, and they were only concerned about the management of their diseases, not the prevention of developing other ailments. People usually undermine the significance of keeping equilibrium in all states of health, which is essential for strengthening the immune system since it can protect them from several diseases. Especially the recent

pandemic of COVID-19 has revealed how vulnerable immunocompromised individuals were (Center for Disease Control and Prevention, 2021; Goldman et al., 2021).

The whole concept of traditional healing is to cleanse the body from everything impeding the maintenance and promotion of good health, causing the human body systems to be compromised; either the cause is physical, mental, emotional, biological, environmental, psychological or spiritual. While the holistic health and CAM approaches stimulate the body's self-healing abilities and immune system, these ancient healing systems incorporate a holistic health approach for nourishing and supporting body tissues and facilitating recovery from diseases. Traditional healing not only depends on interventions but also teaches the person to take responsibility for their body, take some time from their daily schedule and do something constructive for themselves. Ultimately, when a person begins to integrate all those modalities, their body starts giving positive signs and develops the ability to fight diseases better. This book is just a little effort to tell that if a person wants remarkable results for their body, they have to change their lifestyle. They must consume healthy food and drinks, try to include some natural edibles in their diet, do some mild to moderate physical activity regularly and show acceptance for other complementary therapies including acupuncture, meditation, aromatherapy and cupping therapy so that the body can move stagnant vital energies and flush out toxins in a better way; moreover, this book will also tell about the mind-body interventions and ancient concepts of treatment.

Everything must begin with making a few small changes in lifestyle and understanding that it is a long journey; the human body takes time to heal and get healthy. The book discusses how to facilitate the processes of oxygenation, detoxification, bathing, stress management, cleansing of blood and body tissues and strengthening the immune system by identifying the root cause of the diseases. Ultimately, an individual can achieve better health if their focus is not only on the cure of diseases but also on preventing the diseases and getting all body systems in equilibrium.

To all those reading this book, I hope it gives you the same inspiration that its writing has provided me since nature has a lot to offer you, once you have the sense of how you can get closer to nature and reap lots of benefits from it. A person should have to focus more on prevention rather than treatment and take responsibility for their body, mind and soul, as nature has already provided you with self-healing abilities.

Mehwish Iqbal
Dubai, UAE
2021

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I am deeply grateful to all authors who have reviewed, researched and written about all those traditional claims regarding complementary and alternative medicinal approaches since they provide us with ample information; moreover, to our ancestors, who transferred their knowledge for empowering traditional medicine and teaching how to enhance the self-healing abilities in humans with the great emphasis upon prevention.

At CRC Press, I gratefully acknowledge the entire team involved in this book project and in making this edition possible, from development to bringing it to the readers. Notably, my editor Stephen Zollo, who provided me with the chance to write a book for CRC Press and guided me very well at every step; this book wouldn't be possible without his indispensable guidance. Furthermore, Laura Piedrahita for her cooperation and explaining everything in great detail.

Thank you, everyone!

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About the Author

Mehwish Iqbal has acquired her bachelor's degree in Eastern medicine and surgery from Hamdard University, Pakistan, in 2015 and her master's degree in health and pharmaceutical management from Dow University of Health Sciences, Pakistan.

Mehwish is a registered CAM physician and has diverse experience working as a medical content writer, general physician of CAM, product developer and research advisor in the phytopharmaceutical and nutraceutical industry. She has had experience working in various hospitals and pharmaceutical industries since 2015. She has researched, reviewed and written multiple monographs, conference reports, content about pharmaceutical products (including herbal, nutritional, OTC and cosmetic products), health articles and monthly reviews for national and international publishers. She has already been the reviewer of several research and review papers and has developed numerous natural products in the pharmaceutical industry. She has vast experience in treating patients with complementary and alternative medicines, especially with cupping therapy.

She is now working as a licensed doctor of CAM with a speciality in Greco-Arabic (Unani) medicine in one of the renowned health care facilities in the UAE while providing consultation regarding product development to the phytopharmaceutical industries.

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Part 1

TRADITIONAL APPROACHES AND IMMUNITY

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Chapter 1

Concept of the Traditional Medicinal System and Holistic Health

The biggest threats and dangers we face are the ones
we don't see—not because

They're secret or invisible, but because we're willfully blind.

—Margaret Heffernan, 2012

Introduction to the Holistic Health Approach

The word 'wholeness' is derived from the Greek word *holos* while holism from the Greek root is to do with the entire unit instead of any specific part. Socrates once cautioned against managing only one body part since 'the part of the body can never be well till the whole body is well' (Plato). Holistic care is all about considering the whole human being. The entirety of humankind is the total of their mind, body and spirit. The manifestation of both soul and mind, for instance, an individual's determination in rehabilitation or the absolute willpower of the person when overcoming and fighting with a terminal illness, is a vital element of holistic care. Holistic medicine focuses on an individual's ability to be involved in self-care, a kind of promotion for health that is under one's control in such a way as to permit an individual to be a segment of their process of healing.

Therefore, the holistic health care practice accounts for spiritual, emotional, environmental, economic, physical and social features of human experience (Ventegodt et al., 2016). In his controversial theories, Thomas McKeown (physician and philosopher) also put it likewise. The thesis, which dates to the middle of the 20th century, said that physicians gave too much stress on 'cure' and not

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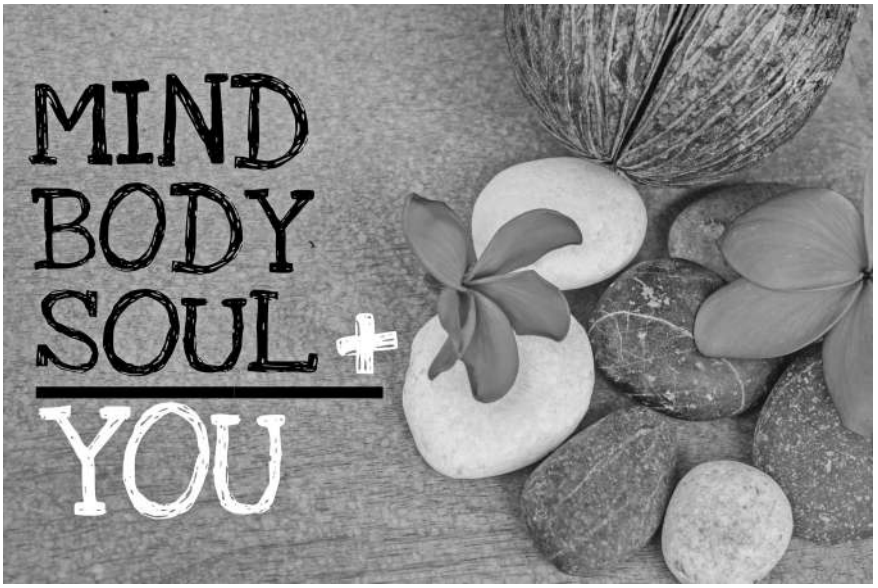

Figure 1.1 Basic concept of holistic health.

adequate on 'care'. Partly due to the misinterpretation of history, 'Misunderstanding of the chief influences, principally personal clinical care, on future and past health improvements has given rise to the mistreatment of resources and misrepresentation of the medicine's role' (McKeown, 1976). McKeown proposed an appeal for a less technocratic and more humanistic role for the profession of medicine. Holistic medicinal care combines alternative and conventional therapies to prevent and manage ailments, and most significantly, to encourage better health. Holistic medicine incorporates all suitable and safe diagnosis and management modalities. It contains an analysis of spiritual, environmental, nutritional, emotional, lifestyle and physical factors. Holistic medicine stresses participation and education of patients in the healing process (Figure 1.1).

Holistic Medicine Principles by the American Holistic Health Association

- Physicians of holistic medicine incorporate a range of effective and safe options in the management and diagnosis, including (a) education for self-care and lifestyle modifications and (b) conventional, complementary and alternative medicines and surgery.
- Exploring the underlying disease's causes is desirable to manage the symptoms individually.
- Physicians of holistic medicine make as many efforts to identify what type of patient has a sickness as they do to identify what type of illness a patient has.
- Prevention, in contrast to cure, is preferable and typically more economical. The most economical approach gives rise to the individual's innate healing capabilities.

- Sickness is regarded as an exhibition of a dysfunction of the entire person, not as a segregated event.
- A principal determinant of healing consequences is the quality of the association recognised between patient and physician, in which patients' autonomy is preferable.
- The ideal relationship between physician and patient reflects the desires, insights, needs and awareness of the patients as well as those of the practitioner.
- The practitioners have a significant influence on patients and they can influence them by their examples.
- Physicians of holistic medicine motivate their patients to elicit the healing power of hope, enthusiasm, love and humour while eliminating the toxic outcomes of greed, hostility, depression, shame, prolonged grief, anger and fear.
- The most potent medicine of life is unconditional love. Physicians make every effort to embrace an unconditionally loving attitude towards patients, other practitioners and themselves.
- Positive health is greater than the absence of disease. It is the mindful pursuit of the highest qualities of the spiritual, physical, mental, social, emotional and environmental characteristics of the experiences in humans (American Holistic Health Association).

Holistic Perspectives and Traditional Medicinal Systems

The beginning of holistic medicine in our recent 'crisis' in health care has been discussed in many aspects differently. It is adequate to state that the holistic medicine concept has ascended when the disease burden in the United States of America has moved from acute diseases to chronic and when increasing costs and multiplying adverse effects are raising queries even regarding the successful management (Gordon, 1982).

The WHO (World Health Organization) has contemplated the traditional medicinal development to execute the slogan 'Health for all' by 2000 AD. The resolution was dependent upon two grounds: initially the lack of primary health care availability to a large number of individuals. Another one is discontentment from the effects of management by modern science, particularly associated with chronic disorders and conventional medicines' adverse effects (World Health Organization, 2002). In 2002, the World Health Organization discussed traditional medicine in great detail (Figure 1.2):

> the comprehensive word traditional medicine is used to refer to traditional Ayurveda, Chinese medicine and Greco-Arabic or Unani medicine, and to different types of ancient medicine. The therapies involved in traditional healing include spiritual therapies, cupping therapy, acupuncture, and manual therapies as non-medicinal interventions, while medicinal therapies include medicines from herbal, mineral and animal sources.
>
> (Lozoya, 1994; World Health Organisation, 2002)

The traditional healing system teaches that vital energy circulates, within and through everything in the universal creations. Energy cannot be demolished;

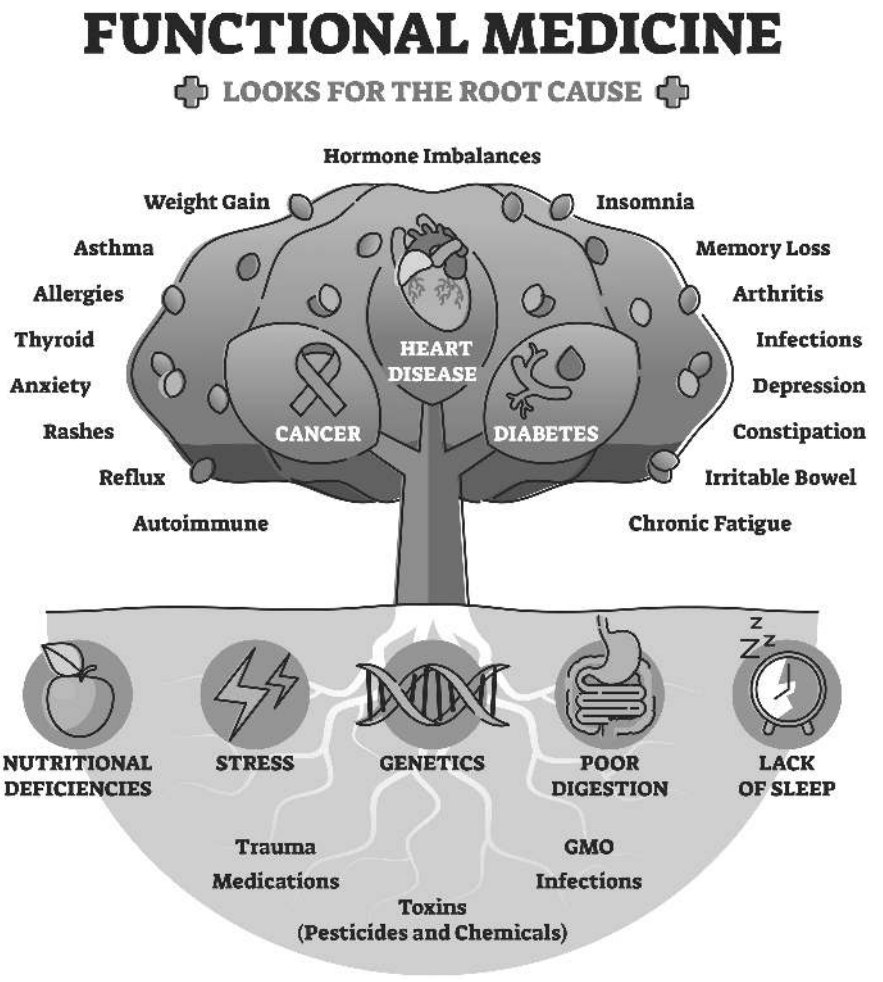

Figure 1.2 Functional medicine as a holistic health approach.

however, it can be influenced adversely, giving rise to illness or flow imbalance. The traditional healing system does not completely perceive disease as poisoning or attack on the body by any external cause. Rather it observes the illness as a state when the body of a human being is unbalanced with its environment. Hence healing is the art of influencing the energy flow to restore the balance in the entire person, instead of just focusing upon the complaint area. In contrast with conventional medicine, spirituality is an essential component of traditional medicine. Traditional medicinal therapy can be quite customised, with every one of the individuals acquiring a different treatment despite identical sickness. While on the other hand, western medicine tends to segregate the human body into different compartments and systems and evaluate functions by investigating the fluids of the body and assessing tissues. Although there is an immense understanding of knowledge concerning the complicated associations of the body, the abnormal features are frequently diagnosed and managed as single units apart from the patient.

The physicians of conventional medicine often subspecialise and perceive disease as an attack on the body by an external creature or the demise of single cells. The emphasis of western medicine is thus to make management available for a particular disease (Pal, 2002).

A remarkable quote by Ludwig Borne (a Greek political author) is that 'There are thousands of diseases yet merely one health'. The concept of health in Ayurveda dates back around 5,000 years and is founded on the balance between *dhatus* (tissues of the body) while the ailment is an imbalance among those tissues. Ayurveda consistently associates body and mind in disease and health (Valiathan, 2011). In accordance with Avicenna, 'health is an active state in which the structure and temperament of the human body are such that almost all of its functions are executed appropriately and healthily'. He also declares the state of balance that an individual enjoys has a specific variety with a lower and upper limit. Particularly, he states that it is similar to an equilibrium that travels amid two maximum limits. While disease, he keeps stating, is an abnormal condition of humans that independently and principally, however not secondarily, interrupts the body's regular functions. Therefore, the disease may be a temperamental or structural disorder (Avicenna, 2014). The traditional system of medicine utilises nature-based products and they are of immense significance. Such kinds of medicine as Ayurveda, traditional Korean medicine, traditional Chinese medicine, Kampo and Greco-Arabic or Unani medicine make use of natural products and have been exercised all around the globe for centuries or even for thousands of years, and they have flourished into organised and regulated medicinal systems. Their different systems may have particular faults, but they are still an esteemed source of knowledge in humans (Alves & Rosa, 2007; Fabricant & Farnsworth, 2001). At the beginning of the 19th century, the period of modern medicine started. In 1805, the foremost medicinally active constituent, morphine, was separated from the plant of *Papaver somniferum* by Friedrich Sertürner (a young pharmacist from Germany) (Hamilton & Baskett, 2000; Joo, 2014). Afterwards, uncountable active constituents have been isolated from natural sources. Amongst them, a number of plants ensue their traditional utilisations while the others do not. Afterwards, the development of artificial techniques caused a considerable decrease in the significance of the natural creations, and there were apprehensions that the utilisation of some nature-based products for therapeutic reasons might be entirely banned (Yuan et al., 2016).

Traditional Chinese Medicine (TCM)

One of the basic sources of doctrine for TCM (traditional Chinese medicine), Nei Ching, gracefully associates the natural impact of lifestyle, diet, environments and emotions with health preservation. The three crucial but simple principles in TCM are (Curran, 2008):

1- Keeping yourself in balance with the environment and nature.
2- Protecting the spirit and the body.
3- Maintaining the balance between inactivity and activity.

There is a popular saying in Chinese, 'one should pay to the doctor only when he gets well, and one shouldn't pay if one is still suffering from illness'; this saying

arises from the philosophy that emphasises preserving wellness all over the life, not just managing diseases when it appears.

The people of China have followed TCM for millennia, and it has its roots in thorough reflection of how the cosmos, human body and nature are interrelated. Traditional Chinese medicine includes a variety of practices of traditional medicine started first in China; these practices include dietary therapy, Chinese herbal medicine, shiatsu massage, Tuina, acupuncture, tai chi and qigong are closely related to traditional Chinese medicine. Principal theories include yin and yang theory, body meridian theory, Zang fu organ theory and Wu Xing's five phases theory (Low & Ang, 2010) (Figure 1.3).

The presence of TCM can be traced by means of inscribed pieces of literature as far back as around 3,000 years. One of the primaeval texts on the subject of traditional Chinese medicine is the Yellow Emperor's manual of medicine or *Ti Nei Ching*. Traditional Chinese medicine is based upon the holistic management approach and an acceptance of the body's ability to come back to its balanced health states, provided the appropriate motivation to do so. The two most significant energies of the body that are required to be in balance are negative (yin) and positive (yang). Both of these forces oppose each other and rule the entire universe. Management is thus carried out by keeping in mind the source of the imbalance which demonstrates itself in symptoms, as compared to addressing merely the symptoms of disease largely and abandoning the cause without correction. It takes into consideration that the human body has a self-healing mechanism, and any intervention should only be made to enhance its self-healing capabilities. The physician at that time had to depend upon the examination of the body surface, the colour of the body's waste product (urine, sputum or faeces), body temperature and pulse (Ellis, 1994).

Traditional Chinese medicine based on the holistic health approach plays a considerable role in enhancing the development of medicine and life science. In the meantime, with the dramatic rise in the frequency of chronic diseases, chemical-based medicines cannot sufficiently satisfy the needs for health preservation or moreover the prevention and management of diseases. Human health stresses the applications and development of natural drugs on a large scale, to which knowledge and experiences of traditional medicines can give a lot. Globally, the ever-rising utilisation of acupuncture and Chinese herbal medicine is a good sign of interest from the public in the Chinese medicinal system. Traditional Chinese medicine is now

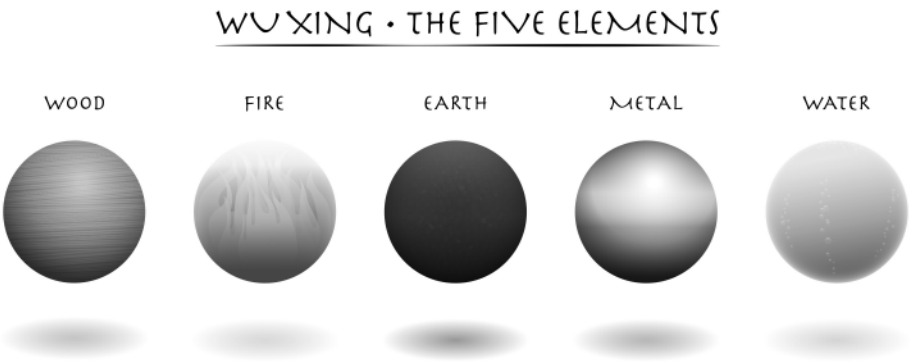

Figure 1.3 Five elements in traditional Chinese medicine.

an indivisible fragment of the public health system in China. Recently, traditional Chinese medicine has progressively acquired substantial endorsement as a part of complementary and alternative systems of medicine in western regions. Chinese medicine, which is the most significant part of TCM, is nowadays utilised in the health care system of around 1.5 billion people globally (Dobos et al., 2005; Qi et al., 2013). It should be observed that in traditional Chinese medicine, numerous ingredients and herbs are blended in accordance with the firm rules to create prescriptions, which are described as formulations (*Fang Ji* in Chinese) (Yuan et al., 2016).

Ayurveda

It is one of the most famous and ancient medicinal systems that has endured and thrived for ages till today. Along with the great knowledge of natural medicine, there is an association between the function and constitution of the human body and the elements and nature of the universe that work in synchronisation and have an impact upon the lives of humans. This system will keep making progress in the coming period. Vedic medicine was originated in India, and the sages of the ancient Indian region utilised their experiences, perception and natural assets to create a unique system of medicine which they called the 'science of life' or Ayurveda. Ayurvedic medicine was originated from the Vedas, the compilation of ancient knowledge. The fourth Veda or 'Atharvaveda' also states several therapeutic concepts and plants from Ayurveda.

Sushruta Samhita and *Caraka Samhita* are the earliest Ayurveda compilations. Ayurveda discusses the unhappy and happy, non-useful or useful aspects of life. According to Ayurveda, health is described as the state of balance between humours (*doshas*), tissues of the body (*dhatu*), hormones, digestive juices and enzymes (*agni*), elimination of waste products (such as urine, faeces and sweat), along with a contented soul (*atma*), mind (*manas*), sensory and motor organs (*indriya*) (Valiathan, 2011; World Health Organization, 2010).

The *Sushruta Samhita* and *Charaka Samhita* are the fundamental writings of Ayurveda; however, they are complemented by a huge number of additions depending upon experiences and observations, none of which influenced the sacredness of the original manuscripts (World Health Organization, 2010). Agnivesha gathered the knowledge he acquired from the Vedas, and it was then subsequently edited by Acharya Charaka and a number of other scholars; nowadays it is recognised by the name of *Charaka Samhita*, which discusses all features of Ayurveda while *Sushruta Samhita* discusses the surgical procedures (Jaiswal & Williams, 2017; Mukherjee & Wahile, 2006; Susruta & Kunja Lal, 2006). Ayurveda is certain that the whole universe is made up of five elements: fire, ether or space, air, earth and water. These *pancha mahabhootas* or five elements are believed to make the three fundamental humours of bodies in different mixtures. These three humours, named *pitta*, *kapha* and *vata doshas*, are collectively recognised as '*tridoshas*' and they regulate the fundamental functions of the human body (Figure 1.4).

Vata dosha causes the transportation between cells, eradication of waste substances and balance in electrolytes, while its outcome is enhanced by dryness. *Pitta dosha* modulates the body's temperature, management of thirst and hunger and coordination of the optic nerve. Conditions of heat in the body exacerbate *pitta*. *Kapha dosha* is enhanced by fatty and sweet food and it lubricates the joints for

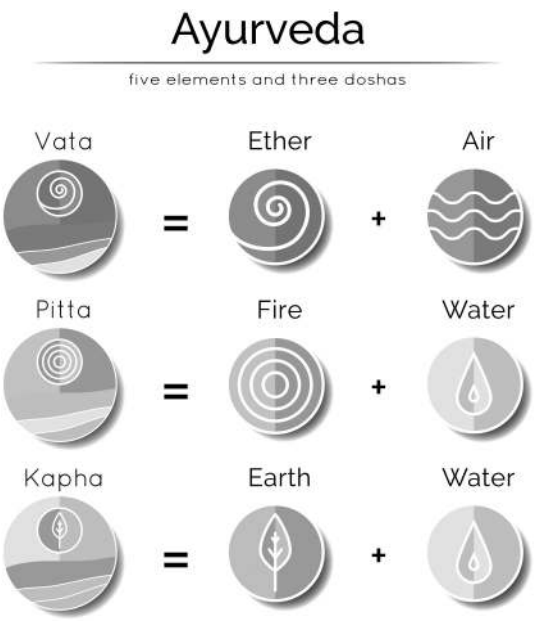

Figure 1.4 Elements and *doshas* in Ayurvedic medicine.

functioning in a better way. The catabolism in the body is assumed to be controlled by *vata*, anabolism through *kapha*, and metabolism through *pitta* (Heinrich, 2004).

An equilibrium between all three *doshas* and related factors should be well maintained for better health and wellbeing. Any discordance among these three *doshas* gives rise to a disease or illness (Ravishankar & Shukla, 2007). Ayurveda supposes that a perfect equilibrium among the natural *tridoshas* and elements of the body should be preserved for living a healthy life by sticking to the fundamentals of divine power (Lad, 1984). The human body is thought to be made up of seven kinds of body tissues known as '*saptadhatus*'. These *saptadhatus* work in coordination with each other for appropriate human body functioning. The blood or *rakta dhatu* modulates the flow of blood cells and supplies blood constituents to the body. The muscle tissue or *mamsa dhatu* gives support in the shape of skeletal muscles for adipose tissues or *meda dhatu*. The *asthi dhatu* consists of the bones, and the *majja dhatu* is composed of the bone marrow and fluids needed for the functioning and oleation of the bones. The *shukra dhatu* is accountable for the reproductive organ's functioning. Aside from the *dhatus* and the *doshas*, the other significant factors contemplated in the doctrine of Ayurveda are the *trayodosha agni* and *trimalas*. The three kinds of waste materials produced in the body because of the digestive and metabolic body functions are called *trimalas*, consisting of sweat, urine and faeces. Ayurveda clarifies that if the equilibrium between all three *doshas* is not preserved, the waste body products will not eradicate efficiently, leading to further disorders such as asthma, diarrhoea, rheumatoid arthritis, constipation and other problems. If urine is not eliminated from the body, it can give rise to urinary tract infections, gastric pain and cystitis, while, if there is no sweating from the body, it can give rise to inappropriate fluid balance and skin irritation.

According to Ayurvedic teachings, the natural fire of the body, which is responsible for all metabolic activities, is known as '*agni*'. There are 13 types of *agni* in the human body, the most essential of which is *jatharagni*, which is accountable for digestive fire. *Jatharagni* is associated with *pitta* and, subsequently, *vatta* in the body. Higher acidity levels in the body boost the digestive fire, resulting in an increase in *pitta* levels and its associated symptoms.

The regulation of natural microflora, efficient digestive activities, and the transmission of energy to the entire body are all dependent on digestive fire. Any disruption in its balance causes discomfort in the gastrointestinal system and can lead to pathological issues such as constipation, ulcers and diarrhoea. Ayurveda provides various therapeutic options for improving individuals' wellbeing based on their physiological constitution, characteristics of *dosha*, pathological history, traits of *dosha*, living style and environmental situations in their daily lives (Hankey, 2001; Jaiswal & Williams, 2017). In its therapeutic strategies, Ayurveda uses the '*panchakarma*' approach. Therapies of *panchakarma* imply several methods for the reinvigoration of the body, detoxifying and increasing longevity. The *panchakarma* is made up of five actions (*karma*) utilised to eliminate the toxins from the tissues of the body. These actions are *vamana* (emesis for therapeutic reasons), *basti* (medicated enemas), *virechan* (purgation by means of using medicine), *nasya* (introduction of medicine by means of the nose) and *rakta mokshana* (blood detoxification). Principally, *panchakarma* comprises of three steps which are *paschat karma* (comprising treatments to be followed to reestablish absorptive and digestive powers of the body and to return to the normal conditions), *poorva karma* (preparatory method for the therapy) and *pradhan karma* (the chief procedure of therapy). In the oleation procedure, clarified butter and therapeutic oils are employed. Sweating (*swedan*) is caused by steam exposure for certain portions of the body to be treated. The consumption of liquorice decoction and honey, followed by a few hours of rice and curd, causes *vamana* or forced emesis since the effect of emesis is thought to be increased by these compounds, while cow milk, senna, castor oil and psyllium seeds are some of the plants and liquids used in a laxative or *virechana* therapy. *Panchakarma* enemas can be made with therapeutic oils or decoctions of plants like anise or sesame (Frawley & Ranade, 2001; Premila, 2006) (Figure 1.5).

Greco-Arabic (Unani) Medicine

Greco-Arabic medicine, also recognised as Arabic, Islamic, or middle-age Islamic medicine, refers to medicine expanded throughout the Golden Age of the Islamic Arabic kingdom, which expanded from Spain (Andalusia) and North Africa (states of Maghrib) in the west to middle Asia and east India, with the central states of Egypt, Greater Syria (Bilad al-Sham) and Iraq playing a significant role. Muslim and Arab doctors and researchers developed a huge and diverse medical literature and incorporated the practice and theory of medicine. According to the primaeval knowledge of Greek and Arabic scholars, temperament is an essential part of creation. Greco-Arab philosophers, for instance, Aristotle and Avicenna, considered that everything in the world is generated from four basic elements, which are symbolically characterised by water, earth, air and fire and with individual qualities connected with all of them. For instance, the element of earth is related to the quality of coldness and dryness, fire with hotness and dryness, water with coldness and

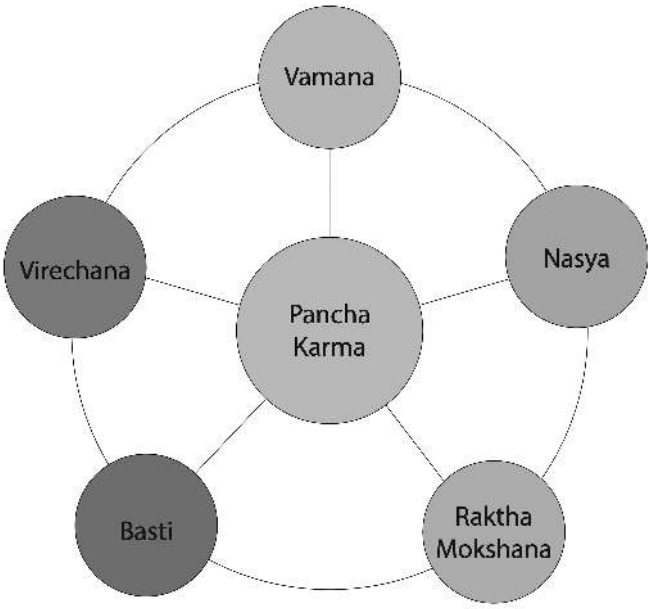

Figure 1.5 *Panchakarma* therapy in Ayurveda.

moistness and air with hotness and moistness (Avicenna et al., 2013). In accordance with the primaeval understanding of the Greco-Arab theorists, an individual's temperament is set and cannot be modified (Bhikha et al., 2015). Unani Ṭibb correlates all of the four temperamental categories recorded above with qualities. This indicates that each one of the temperamental types has a mixture of the four qualities of heat, coldness, moistness and dryness. Every person is an amalgamation of whole four temperaments (Figure 1.6).

In Greco-Arabic medicine, the six essential factors for health conservation are movement and rest, fresh air, sleeping and awakening, food and drink, retention and elimination, mental movement and rest (Ayni & Umar, 2009). Arabic medicine was primarily built on customs, principally the practical and theoretical understanding extended in Mesopotamia, Arabia, Rome, Persia, Greece and India. The initiator of the Arabic-Islamic medicine is considered to have been the Prophet Muhammad (PBUH) himself, as a considerable number of Hadith (declarations by the Prophet) with reference to medicines are attributed to him. His statement that 'there is no illness that Allah has made, apart from that He also has made its management' gave confidence to the Muslims and Arabs to keep themselves in medical research and try to find out a cure for all diseases identified to them, and thus instigated the foundations of Greco-Arabic Islamic medicine. The medicine of Egypt dates from around 2900 BC; however, the top known pharmaceutical record of Egypt is the Ebers Papyrus which originates from 1500 BC. This manuscript presents some 700

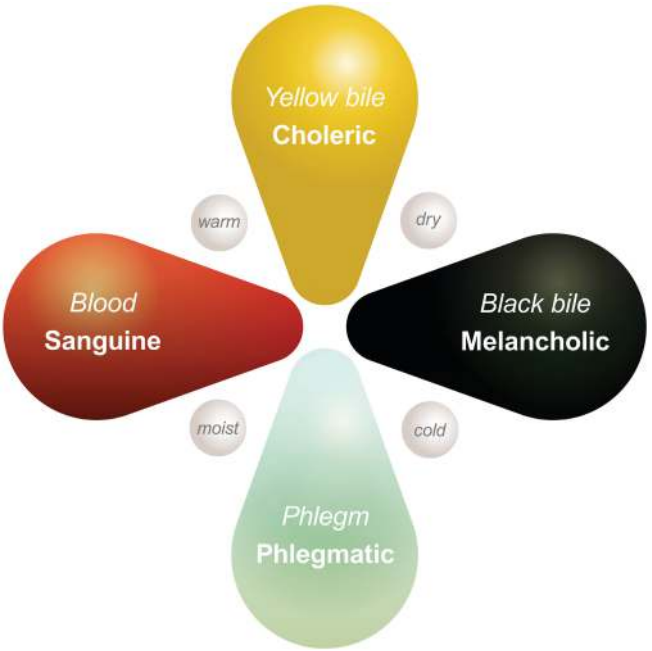

Figure 1.6 Four temperaments in Greco-Arabic (Unani) medicine.

animal and herbs-based drugs and consists of formulas, for instance, poultices, gargles, infusions, snuffs, pills and ointments, with honey, milk, beer and wine, and is frequently used as means of transportation of medicines (Morgan, 2008; Pormann, 2008; Saad & Said, 2011). By the 6th century, Arabia had created economic links with primaeval civilisations, for instance, Phoenicia, Egypt, Assyria, Persia, Greece, Rome, India and Byzantium, with a deal in valuable frankincense, spices and myrrh. Rhazes is regarded as the best of all Muslim and Arab researchers, alongside Albucasis (Al-Zahrawi) and Avicenna.

Ibn e Sina or Avicenna (980–1037 CE) was birthed in Afshana, a small village in Bukhara's outskirts (Sahni, 2016). Around 240 publications, articles and treatises in numerous scientific and literary subjects survive from Avicenna's efforts (Rafiabadi, 2005), among which the *Kitab al-Qanun fi-al-Tibb*, also recognised as the *Canon Medicinae* (codes of laws and Greek principles), is by far the greatest, most renowned, and most significant of his works in the field of medicine, as well as the most meticulously protected treasury in both the Latin and original Arabic version (Tschanz, 2003). The famous British writer Colin Ronan referred to it as 'the foremost textbook of medicine on the planet' (Ronan, 1984). The concepts stated within are still studied as a segment of medicine's history at universities such as Yale University and University of California among others' (Hajar, 2013). 'Medicine is the study of science by which we understand the several states of the body; when in health, when not in health; the ways by which health is susceptible to loss; and when lost, is expected to be recovered' (Avicenna & Gruner, 2014). In other words, according to Ibn Sina, 'it is the skill of maintaining health and restoring it after it has been lost' (Avicenna & Gruner, 2014).

The Seven Health Preservation Doctrines for maintenance of health, described by Avicenna, are mentioned here (Avicenna & Gruner, 2014):

1. Temperament equilibrium.
2. Choosing health-preserving food and drink.
3. Elimination of noxious substances.
4. Keeping the composite safe.
5. Making sure that the air we breathe is pure.
6. Protecting against unanticipated events.
7. Limitation in physical and mental movements, including 'waking and sleeping'.

Avicenna, a devout Muslim with a thorough understanding of the Holy Quran and Hadith, used the instructions included therein profoundly in his own medical practice, whether scholarly, preventive or therapeutic. 'Seek [Allah] for health and forgiveness, for after being given assurance, one is provided nothing superior but health', according to a genuine Hadith (Khan et al., 2015). In humans, the goal of maintaining this blessing can be achieved by gaining an extensive understanding of the principles of acquiring and retaining health, as well as adhering to the holistic guidelines for consuming healthy foods and beverages, keeping away from unhealthy activities, and promoting environmental, general and individual hygiene. Preserving the equilibrium between the promotional and preventive aspects of medicine is essential. Another authentic Hadith explains the concept of health potential: 'And preserve enough health to call on throughout your disease' (Leaman, 2008).

Better immunity, proper nutrition and overall fitness are all elements of health potential that enable an individual to function well with the stress that the individual may experience (Al Khayat et al., 1997). In accordance with Avicenna, 'the well being of the whole person – emotionally, physically, spiritually and mentally – is necessary for the believer to participate fully in life, fulfilling their duties towards a better society' (Avicenna, 2014).

Ṭibb al-Nabawi (prophetic medicine) emphasises the management of ailment or the removal of disease and the preservation of health. 'There are two types of sickness: disease of heart and disease of the body'; both of them are reported in the Holy Quran. Ṭibb al-Nabawi (prophetic medicine) focuses upon both the body's disease and the disease of the heart. The disease of the heart relates to the soul, which resides in the heart, rather than the physical heart. The disease of the heart is of two types: disease of doubt and uncertainty and disease of temptation and desire. Prophetic medicine provides the details of dietary modifications as well as the limits in which Islam shows human beings to appreciate the pleasures of life, counting food and beverages. 'The Adam's son merely requires some bites that would keep them alive, however, if he insists, 1/3rd should be kept for his food, one more third for his beverage and the last 1/3rd for his air' (Bhikha et al., 2015; Ibn-Qaiyim al-Ğauzīya & Zeni, 2016).

Traditional Medicinal and Holistic Approach for Maintaining the Health of the Immune System

Immune cells are distributed into those of the adaptive and innate immune response. The innate immune reaction is the primary reaction to attacking pathogens. Innate

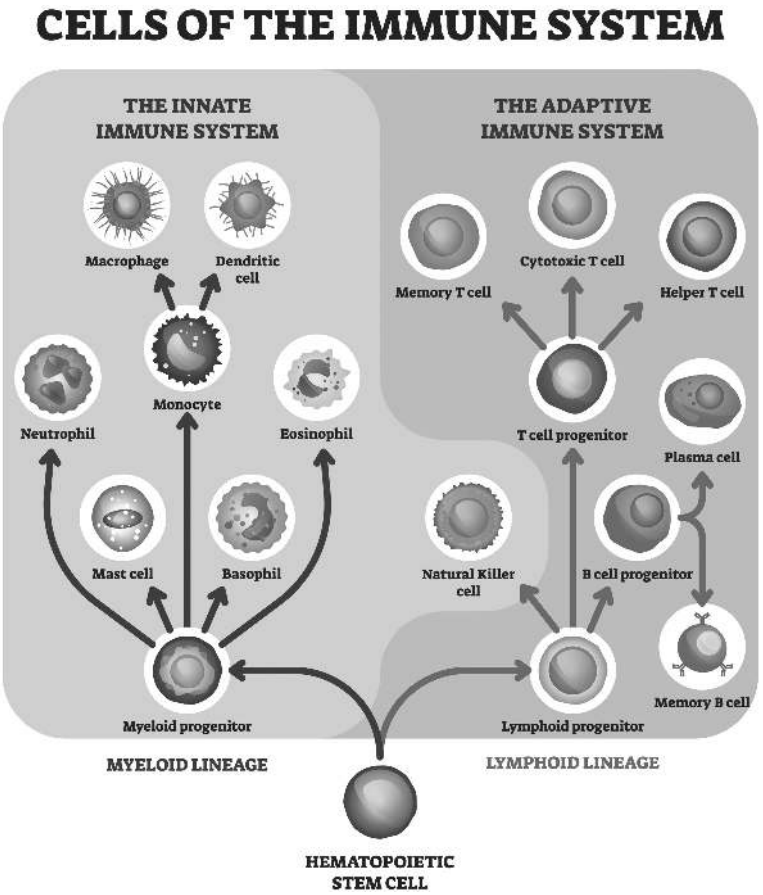

Figure 1.7 Cells of the human immune system.

immune cells include monocytes, macrophages, dendritic cells, eosinophils, mast cells, neutrophils, etc. The immune system's innate response is prompt, however not customised, and in general, it is less efficient in contrast with adaptive immune reactions (Figure 1.7).

The adaptive immunity can identify a pathogen or antigen and 'memorise' it if it is confronted again. T-lymphocytes play a crucial role in antigen detection and immune reaction coordination. T-lymphocytes are available in many subtypes that help coordinate with various kinds of immune reactions. T-lymphocytes are divided into cytotoxic T cells and helper T cells which are included in the direct destruction of infected and destroyed cells or tumour cells. Helper T cells have the CD4 receptor and are involved in coordinating immunological reactions.

Helper T cells are classified into different types based on their cytokine levels. Helper T cells type 1 synthesise interleukin-2 and IFN-γ and are engaged in cellular immune and antiviral reactions, and the helper T cells type 2, which create interleukin-3, interleukin-4 and interleukin-5, are engaged in anti-parasitic and humoural reactions (Romagnani, 2000). Hence, T cells are responsible for putting together a suitable immune reaction in response to immunological challenge or stimulation,

while the B cells, which are accountable for the synthesis of immunoglobulin or antibodies, are the other lymphocytes of the adaptive immune system.

Igs are molecules that are particular for the pathogen and assist the immune system in identifying and damaging disease-causing agents. B cells, just like T cells, particularly react to an antigen. They can distinguish into plasma cells, lasting only for a short duration, which synthesises Igs in the short period or can turn into plasma cells that can live long. The B cells can transform into plasma cells, which synthesise any one of five types of antibody (IgA, IgG, IgE, IgD and IgM); each type of antibody has a dedicated role (Schroeder & Cavacini, 2010).

B cells and T cells can particularise to turn into memory cells, which continue permanently or for extensive durations and can identify the antigen if experienced again, subsequently provoking a swift immune response that is pathogen-specific. An exploding immune reaction is catastrophic with regards to energy spent and results in deterioration of the tissues in the host; hence rapid and absolute rectification of an immune reaction is also important. Cytokines are involved in the resolution of immune reactions, while interleukin-10, which is synthesised by a variety of immune cells counting regulatory T cells, has anti-inflammatory activity and is included in subduing the synthesis of inflammatory cytokines (Saraiva & O'Garra, 2010).

The incitation of an immune reaction and immune cells' activities results in the signs of inflammation, i.e. pain, redness, heat sensation and swelling, which represents the deterioration of the tissue occurring during the functioning of the immune system. There is a rising concern that contemporary lifestyle modifications have resulted in the stimulation of continuous low-grade systemic inflammation because of the involvement of immune cells and other cells of the body, such as adipocytes. This kind of exposure may include quantity and quality of diet (Childs et al., 2019).

The system of immunity is progressively established to be included in the numerous chronic diseases development, for which conventional medicine has given restricted methods for prevention and management. In that circumstance, it seems valuable to target immunity in order to control the risk of particular chronic diseases. Simultaneously, organic health products are giving rise to revived interest, especially in preventing and managing numerous chronic ailments. The immune system, if over-activated or under-activated, can generate multiple disorders in the body. Chronic inflammation can trigger considerable non-specific devastation of surrounding tissues. In point of fact, the immune system and inflammation are closely tied. Moreover, inflammation is progressively established to be included in the development of numerous chronic disorders like neurodegenerative disorders, arteriosclerosis, cancer and diabetes.

Dysfunction of the immune system has also been associated with disorders such as depression, anxiety and chronic pain, although at times as a result instead of a cause, and may be included in other processes of disease in a way that is not entirely understood in the recent era. Throughout the previous century, contemporary medicine has made significant progress in sanitation, vaccines, antibiotics and other initiatives of public health. These efficiently impede the development of contagious diseases among the population. In point of fact, contemporary medicine best succeeded in managing acute diseases. It is in the domain of chronic ailments that modern drugs have been quite dissatisfying and that natural health products have generated revived interest. Natural health products include herbal medicines, minerals, vitamins, animal-based products, prebiotics and probiotics (Haddad et al., 2005).

Complementary and alternative medicines were frequently used to manage musculoskeletal pain, colds, chest congestion, depression, anxiety and muscle stiffness. There are lots of reasons why therapies of complementary and alternative medicines are famous. Management of biochemical and physical indications of diseases is not the only objective of CAM physicians but also to consider the spiritual, social, emotional and nutritional context in which the disorders emerge. The utilisation of techniques of mind-body and body-dependent interventions is relieving and can decrease stress. Moreover, several natural products can be brought from supermarkets and organic food shops, as natural products have frequently been consumed for hundreds of years; they claim to be efficient yet harmless in contrast with conventional drugs.

Complementary and alternative medicines give control of the patient's own health to them. Amid lots of mechanisms by which complementary and alternative medicinal approaches are stated to function, their claimed effects on the immune system resonate with the modern recognition that health considerably relies on the competence of the immune system. Even prior to the notion that the immune system was connected, practitioners of vitalism, such as naturopathic doctors, asserted that sickness should be managed by invigorating the capacity of the body to treat itself rather than managing only symptoms. It can be now believed that cancers and infections can be an effect of deprivation in optimal surveillance of the immune system.

There are lots of publications discussing the management efficacy of complementary and alternative medicinal approaches that are assumed to mediate their outcomes by means of the immune system, all documenting diverse ranges of verifications which range from case studies and anecdotes to extensive RCTs. A group of nutritional supplements works as immunomodulatory nutrients since they have the ability to regulate immune system activity (Hughes, 2001). Amid them, the most researched are vitamin E, vitamin A, omega-3 PUFAs and zinc. Nutritional supplements like vitamin E can give an indispensable external source of antioxidants; deficiency of vitamin E is related to reduced B cell and T cell mitogenesis (Langweiler et al., 1981), decreased activity of natural killer cells, synthesis of interleukin-2, and phagocytosis of neutrophils in both humans and rodents. On the other hand, vitamin E supplementation enhances mitogenesis of T cells, the activity of natural killer cells (Moriguchi et al., 1990) in rodents, antibody synthesis in mice (Tengerdy et al., 1973), synthesis of IL-2 (Bendich et al., 1986) along with B cells and T cells mitogenesis (Yasunaga et al., 1982). Deficiency of vitamin E is aggravated in malnourished elder people (High, 2001). Vitamin E supplementation for older adults in therapeutic doses boosts their immune responses. On the other hand, deficiency of vitamin A extensively damages innate immunity by inhibiting the function of NK cells, macrophages and neutrophils (Dawson et al., 1999; Wiedermann et al., 1996). Moreover, deficiency of vitamin A decreases reactions of antibodies directed by helper T cells type 2 (Th2) and hinders the typical restoration of barriers in mucosae that are destroyed by infections of viral origin (Stephensen, 2001).

Probiotics, which are originated from the Greek term indicating 'for life', are nutritional supplements that include beneficial microorganisms (in the form of milk, capsules, fortified yoghurts and powders) for health preservation and are commonly used to manage urogenital and gastrointestinal tract infections (Alvarez-Olmos & Oberhelman, 2001). The most frequently found probiotic bacteria are *Bifidobacterium* and *Lactobacillus*. Atopic diseases, diarrhoea in adults and children, urogenital infections and inflammatory bowel disease have all been studied with probiotics.

Mind-body interventions are concerned with the relationships between the mind, soul, behaviour and body, as well as the profound effects that spiritual, emotional, behavioural and mental aspects can have on health. Abnormalities in the immune system have been linked to a variety of disorders and stress, according to experts in the field of psychoneuroimmunology (Kiecolt-Glaser et al., 2002). By means of the sympathetic adrenal medullary axis and the hypothalamic-pituitary-adrenal axis, psychological stress can influence the immune system (Yang & Glaser, 2002). A review of the literature (Astin et al., 2003) demonstrated moderate verification of efficiency for mind-body therapies like visualisation, meditation, relaxation, hypnosis and biofeedback for the management of insomnia, coronary heart disease, incontinence, persistent lower back pain and headache. A meta-analysis of 85 experiments, however, found only limited evidence that these therapies can reliably affect immune responses (Miller & Cohen, 2001).

Conclusion

Nowadays, it is well-identified that modern medicine has principally emphasised what can be measured and observed. Though this methodology has given rise to huge advancements in medical and technological fields and offers remarkable benefits to lots of people, the things that are visible are merely considered the tip of the iceberg and the considerable part of the iceberg rests well beneath the surface; similarly, it applies to humans: below the physical area there lies a productive ground for research that can give significant payoff.

We've fortunately become constantly able to dig deeper under the surface, particularly into the genetic and molecular components of disease, due to the advancement of better and more powerful technology. This, however, overlooks people's complex spiritual, mental, social and emotional dimensions, all of which influence not just their beliefs, thoughts, feelings and stronger emotional facts but also their physiology. This is also true for most approaches to complementary and alternative medicines, which, while often more holistic in nature, are still centred on symptomatic relief, specifically as CAM implemented currently under integrative models of care. The therapeutic approaches having multiple dimensions will embrace a much more significant, more profound perspective in the future. It will completely identify and recognise the underlying emotional, mental, spiritual and social elements of one's being, which have a significant impact on all aspects of one's health and life.

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Chapter 2

Role of Nutrition and Diet Therapy in Boosting Immunity

Introduction

Diet has a significant impact on human health and has been a research topic for a long time, from its influence on the evolution of humans throughout the Palaeolithic era to its role in giving rise to diseases such as cardiac ailments and diabetes (Fairweather-Tait, 2003).

The human body is composed of trillions and billions of cells which work in a synchronised way to execute any function. These cells need a sufficient amount of nutrients and wholesome food to work, and when the consumed diet is not capable of fulfilling the demand of the body for essential nutrients, then people start developing diseases. Not merely the habits of eating but other daily activities are also accountable for causing other lifestyle disorders. It has been established that noninfectious diseases cause nearly 41 million deaths each year which is approximately 71% of all fatalities around the globe (World Health Organization, 2021a). The advancements and industrialisation in aspects of technology made the standard of living better for humans though it is also accompanied by disadvantages that can't be overlooked. Modern ways of living are contemplated to be rapid where the individual thinks about money first, even before their wellbeing and health. The rising trend of fast food and technological advancements has made people lazy in doing all physical activities, and lack of physical activity along with escalating stress have enhanced the ageing process and development of new ailments. Moreover, the disorders that were generally noticed among the population of old age can now be observed among younger individuals. At the same time, the worsening quality of food along with lack of adequate nutrition has enhanced the process and has given rise to the appearance of several complications of health at an extremely early age. The disorders related to lifestyle have a serious influence on human health. The lifestyle evolution has resulted in the appearance of several metabolic and cardiac diseases, which are

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predominantly related to obesity and other lifetime diseases such as diabetes (Singh et al., 2020) (Figure 2.1).

The idea of consuming foods that naturally or by means of supplementation give benefits to the immune system is not unique. Four thousand years ago, Egyptians started using honey known as *Leptospermum* honey (manuka honey) for the management of wounds; honey bees that gather nectar from jelly bushes and manuka in New Zealand and Australia are now grown as a honey source that is stated to have the capability of decreasing infection and alleviating sore throat and flu symptoms (Smith & Charter, 2010). The people who are worried about the prospective adverse effects of modern pharmaceutical medicines have begun to search for more organic forms of prevention and management. It has also been demonstrated that a great proportion of hospital cases are malnourished, which affect the functions of the immune system (Girodon et al., 1999; McWhirter & Pennington, 1994). It is generally accepted that there is a considerable burden of disease in people because of the impairment of the immune system, e.g. asthma, rheumatoid arthritis and inflammatory bowel disease (IBD) (Girodon et al., 1999; Grimble, 2001; Navarro-Alarcón & López-Martínez, 2000). At least 90 nutrients are required for life's sustenance, including 16 vitamins, 63–74 minerals and trace elements, three essential

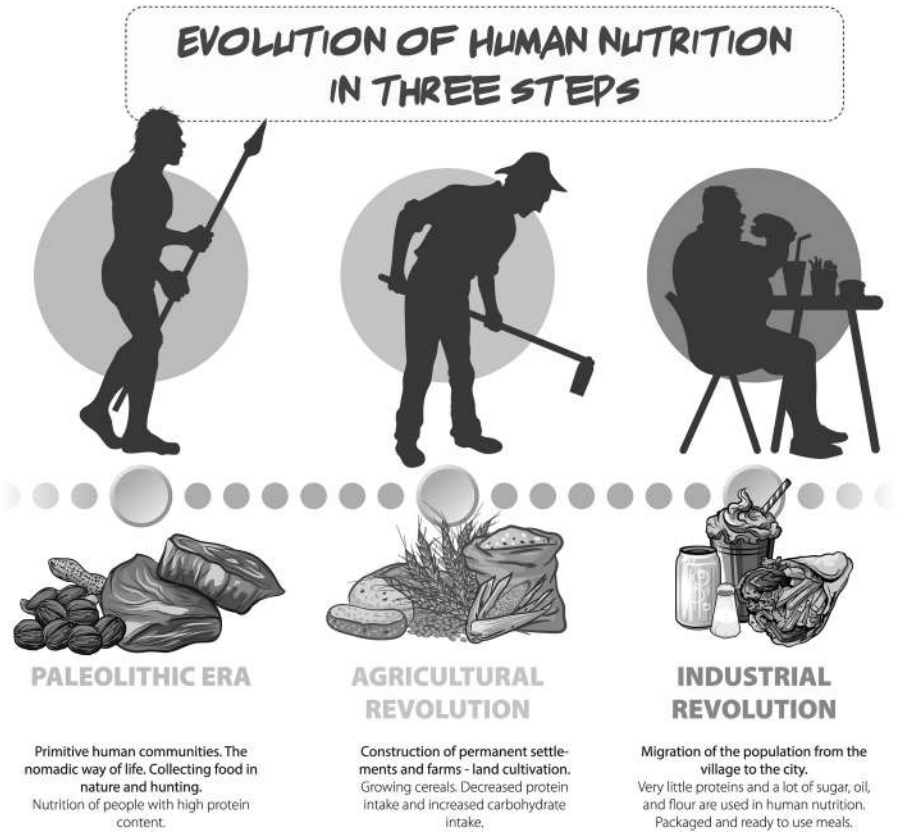


Figure 2.1 Dietary evolution in humans.

fatty acids and 12 amino acids. It is significant to observe that lack of minerals can impede the utilisation of other nutrients. On the contrary, pure molecular mineral forms are too big to be absorbed (Smith & Charter, 2010). Therefore disruptions in the status of nutrition put forth a considerable impact on the immune system's competence and can cause a rise in vulnerability towards infection through the lack of nutrients, or persistent inflammation related to over-nutrition (Afacan et al., 2012). A study regarding the regulation of immune function by diet in individuals ranging from a healthy subject to those with compromised functions of immune systems has reinforced the overall results that foods have the ability to have an impact upon the acquired or innate immune systems. Showing efficiency for managing disorder in compromised persons, preventing ailments in those who have good wellbeing and assessing nutrition and its intricate outcomes on immunity; all these factors have come up with a rising discipline commonly recognised as 'immunonutrition' (Kaminogawa & Nanno, 2004).

Hence, nutrition plays a considerable role in prevention, particularly among ageing people that show diminished immunity and increased susceptibility for disorders such as type 2 diabetes mellitus, hypertension, cognitive weakness and cancer (Gupta & Prakash, 2015). For instance, resveratrol is a polyphenol naturally found in plants such as berries and grapevines. Resveratrol has antioxidant properties and has considerable healing potential for the management of inflammatory diseases. Managing peripheral mononuclear cells in blood with resveratrol decreased the production of inflammatory mediators by innately stimulated leukocytes, hence supporting and characterising its strong anti-inflammatory effects (Fordham et al., 2014). Immune-mediated disorders are more common in 'western' countries with a raised burden of disease, which is often attributed to commonly consumed dietary components such as greater consumption of added sugars, total calories and fat, while on the other hand, a minimum intake of fibre and a diet with imbalanced fatty acid content (Schulze et al., 2018; Schwingshackl & Hoffmann, 2015).

The chapter focuses on the traditional aspect of diet therapy, the history of the Palaeolithic diet and what its status is in the current era, contemporary nutritional approaches and what deficiencies of certain nutrients can cause to the body, weight management and disease prevention, the importance of polyunsaturated fatty acids in preventing metabolic and cardiovascular diseases and some of the healthy foods.

Diet Therapy in Light of Eastern Medicine

'Food', ethno-biologically, can be categorised as:

> 1. Principal food, which fulfils the hunger; 2. Additional food, the form of food that can be consumed as subsidiary to the principal item of food (such as salad, fruits, and nutritious drinks); 3. Food products—this class should consist of: (i) Counteractive food; (ii) Ingredients of Food. (Goswami & Ram, 2017)

This dates to the old literature of India such as the *Manusmriti*, *Ramayana* and *Bhagavadgita*; each community that existed in India had a visible and individual system of belief for food. A number of these, though, have been affected by the practices and beliefs of Aryans. In accordance with the beliefs of Aryans, food was contemplated as God's gift and a source of strength (Achaya, 1994). In the Vedic era,

religious songs, knowledge, poems and prayers were inscribed, which appeared to be recognised as Vedas. The Vedas are a significant category of spiritual texts in the classical literature of India. The four Vedas, specifically the *Rigveda*, *Yajurveda*, *Atharva Veda* and *Samaveda*, discuss various cereal grains and their day-to-day consumption. The Aryans assumed that food was not only meant for the nourishment of the body but was the fundamental part of a virtuous cosmic cycle (Achaya, 1994). *Hordeum vulgare* (barley) appeared as the primary staple food of Aryans and is also stated in the *Rigveda*. The texts that were written afterwards mentioned sugarcane, lentils, wheat and millets; the khichdi prepared from lentils along with rice is extremely nutritious. Aryans were aware of the cultivation of rice and desiccated cereals; there was a typical way of processing rice throughout this period. Rice and lentils were the blends of complementary nutritional elements used by Aryans (Sen, 2004). The Jain and Buddhist literature shows the considerable use of rice and its thin porridge (gruel). According to Ayurveda, foods are traditionally categorised into three principal classes, i.e. (i) satvik foods (including milk, honey, cooked vegetables and fresh fruits which are intended for the sages and are beneficial for health), (ii) tamasic food (foods that incite the lowest, stupid qualities of behaviour in humans such as garlic, liquor, onions, meat, sour and spicy foods), and (iii) tajasic foods (including the food that gives sufficient energy to perform day-to-day work) (Dubey, 2011).

Ayurveda taught that every human has self-healing power, though diet should be preferred according to the constitution of the human body. If a person identifies their body type (*vata/pitta/kapha*) and what kind of food is associated with the constitution of the body, then it will be easy to choose the proper food items for consumption. One must have to consider other factors as well, such as the seasons, tastes, heaviness or lightness of food. Foods such as ice cream, melon, potatoes, peas, beef and apples aggravate *vata dosha*, so the individual with *vata* body constitution shouldn't consume these foods in excess quantities, while brown rice, sweet fruits, coconut, grapes, avocadoes and oranges are useful for people with *vata* body type. Considering the combinations of diet, specific food items shouldn't be consumed together, such as milk with fish, milk with sour fruits and milk with beef, because these combinations can create an imbalance in *doshas* (humours of the body), ultimately resulting in the production of toxins (Lad, 1984).

The Greco-Arabic or Unani medicine also greatly emphasised diet. As Avicenna stated, 'A number of diseases only emerges from prolonged and persistent inaccuracies with regimen and diet; moreover, he proposes that the process of digestion should be observed as a process by which edibles are cooked or heated by the body'. Numerous considerations and factors are present regarding diet, though the one most significant is that foods should be chosen appropriately so that they can maintain the balance among all four body humours and should be in accordance with the temperament of the person; moreover; suitable for the climate, season and age (Avicenna, 1999).

According to Tibb (Bhikha, 2017)(Commonly recognised by the name of Unani, medicine is an extensively practised traditional medicinal system, and it has its deep roots in Greek medicine, which is based on the principles of Hippocrate, Galen and Avicenna), the dietary value of any food is determined by the quantity and quality of every humour it produces. Verification of the scientific rationality of the Greco-Arabic (Unani) Tibb for metabolic effectiveness of digestion and foods is established in research conducted upon enzymes by Dr Edward Howell, MD, who is the leading global expert on the activity of enzymes in the digestion of food.

Dr Howell's wide-ranging research on enzyme nutrition validates that around 80% of the activity of an enzyme is dedicated to food digestion. However, all of the enzymes confined in uncooked foods are destroyed by radiation, boiling, freezing and frying; a number of people take food that has no content of enzymes at all. The research conducted by Dr Howell also demonstrates that when the spices of hot temperament such as cinnamon, ginger and cumin are taken, the synthesis of digestive enzymes by the body raises dramatically. Even more significant, whenever the body has gone through fasting, enzymes usually allocated by the body for food digestion are free to conduct the functions of healing, such as dissolving the dormant tumours. This esteemed research by Dr Howell validates the value of traditional medicine, as the spices and edibles with hot temperament cause a rise in digestive enzymes, an escalation in metabolic functions of cells and ensure complete absorption of micronutrients with little metabolic waste (Chishti & Chishti, 1991; Howell & Murray, 1985).

Palaeolithic Diet

Four basic periods of modifications in the diet of humans have caused considerably changed patterns of food expenditure and consumption: (1) the pre-Paleolithic, (2) the Paleolithic, (3) the Neolithic and (4) the industrial revolution period. A great number of shifts in society have meant that humans of the modern era take significantly more calories in contrast with their ancestors (Jones & MacKay, 2010). The Stone Age, or the Palaeolithic era, commenced nearly 2.5 million years before the present when initially humans started using stone instruments. The era finished with the commencement of agriculture in the Neolithic era around 10,000 years ago. Throughout the Stone Age, wild meat, fruits, eggs, nuts, berries, fish, vegetables and insects were taken in different quantities depending on the environmental niche (Lindeberg, 2005; Lindeberg et al., 2003) (Figure 2.2).

In the Palaeolithic diet, the comparative contributions of fat, carbohydrates and proteins to total energy were assessed to vary from 28 to 58%, 22 to 40% and 19 to 35%, respectively (Jones & MacKay, 2010), with comparatively high content of monounsaturated fatty acids and polyunsaturated fatty acids but with low ratios of ω-6/ω-3 fatty acids. Meanwhile, today the distribution of micronutrients has changed; fat has gone up as high as 42% of total energy intake, with extremely high levels of saturated fats and ω-6/ω-3 fatty acid ratios in contrast with those observed in the hunter-gatherers' diets (Bang et al., 1980; Uauy & Díaz, 2005). Greater than 4,000 generations of human beings survived as hunter-gatherers, followed by 500 generations that relied upon agriculture. There have been merely ten generations from the beginning of the Industrial Age, and only two of these have been raised by consuming extremely processed foods (Eaton & Konner, 1985). Nowadays, less than 12% of Americans consume the five regular servings of vegetables and fruits advised by dietary guidelines (Casagrande et al., 2007). Apart from that, even the population who daily consume vegetables and fruits usually restrict themselves to rather unexpanded food choices (Jones & MacKay, 2010).

Metabolic syndrome, overweight and obesity have been evidently absent in people of the 20th century with Stone Age or Palaeolithic living styles, as demonstrated in numerous surveys. Disorders of the cardiovascular system, including stroke, were seemingly unidentified in Eastern parts of Africa before the evolution to contemporary lifestyle (Lindeberg, 2005). Hunting and gathering habits of our

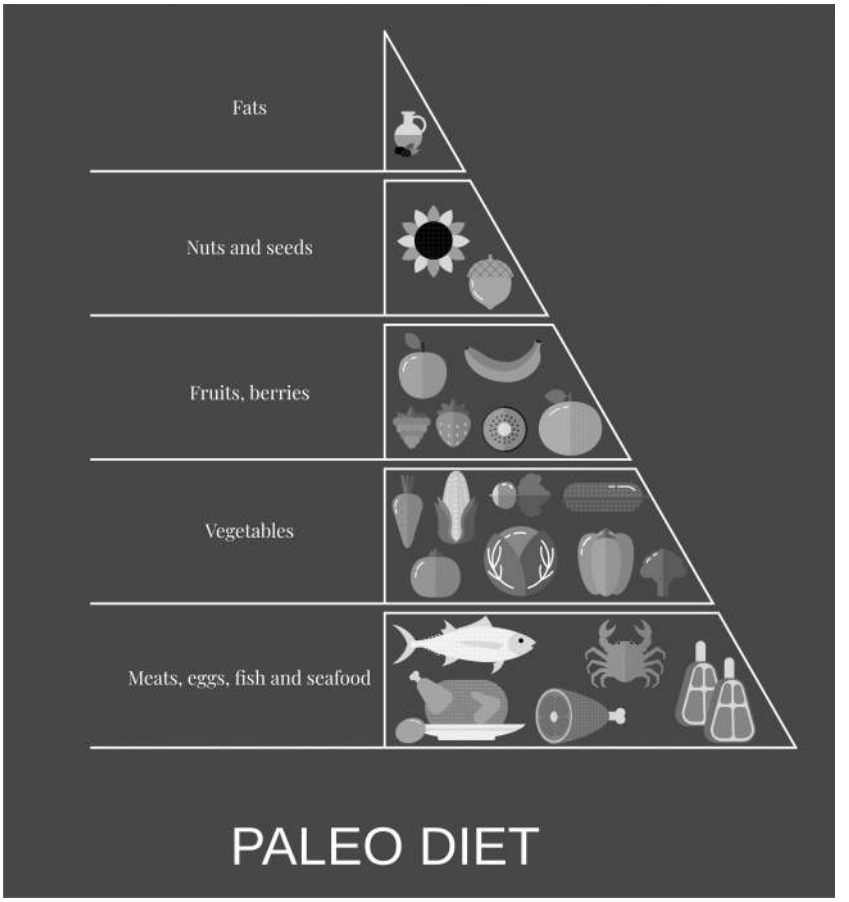


Figure 2.2 Palaeolithic diet.

forefathers necessitate substantial physical exertion, indicating that they exercised daily, likely to lower the levels of lipids in blood and burn their fat—skeletal remnants specified that hunter-gatherers were quite muscular compared to humans of the modern era (Eaton & Eaton, 2003). Palaeolithic diets specify that high fibre, low energy and low-fat patterns are appropriate. While significant in moderation, cereals and dairy should not be taken in excess. It is also evident that modern patterns of energy expenditure require to be escalated, and regular physical activity is recommended. Balance in calories represents a fundamental process of making sure that the total energy consumed is equivalent to the total net energy used. In this manner, weight gain can be prevented (Jones & MacKay, 2010).

Traditional Ways of Meal Consumption

Several people believe that consuming food with hands is disturbing, unhygienic and primitive; though according to traditional eastern culture, eating food with

hands is related not merely to the body but also to the soul and psyche. Consuming food with hands provides both mental and physical health and satisfaction. In accordance with the Vedas, the toes and fingers of humans resemble *pancha mahabhoota* (five elements). The little finger is related to water (*jala*), the ring finger to earth (*prithvi*), the middle finger to ether (*akasha*), the first finger to air (*vayu*) and the thumb is associated with fire (*agni*) (Hegde et al., 2018) (Figure 2.3).

Discussing the serving dishes for food, many Indian families utilise various leaves for consuming food. Leaves were the most initial plates utilised for food serving. Because of the times when humans were living in forests, leaves have been utilised for different purposes, including food consumption. Various organic reserves even now provide food on leaves. Consuming food on leaves is savvy and wiping the mess after food consumption is easy. The utilization of banana leaves for food serving antedates to a period before the use of metals turned out to be the backbone of cutlery. Utilising fresh leaves was considered more expandable and sterile than utilising wooden utensils. Since banana leaves are thick, huge and limitless and they don't puncture easily. Banana leaves consist of numerous polyphenols, a distinctive cancer-preventing constituent found in most plants (Hegde et al., 2018) (Figure 2.4).

The posture of sitting during the consumption of food also plays a part in the preservation of health as consuming food while sitting on the floor has numerous benefits and is still famous in various Asian countries. The notion is that one should value the process of eating with the highest number of senses such as touch, smell, taste and sight. When people sit on the floor, whether it is *sukhasana* or *vajrasana* (Figure 2.5) or any other yoga posture, a considerable number of muscles are utilised contrasted with when a person is sitting on any seat. When a person sits with their legs folded on the floor, the cardiac system can function well with better distribution. Moreover, it provides great strength to the lumbar region, inhibiting distress and torment.

Figure 2.3 Eating food with hands in the Indian subcontinent.

Figure 2.4 Meal served on a banana leaf.

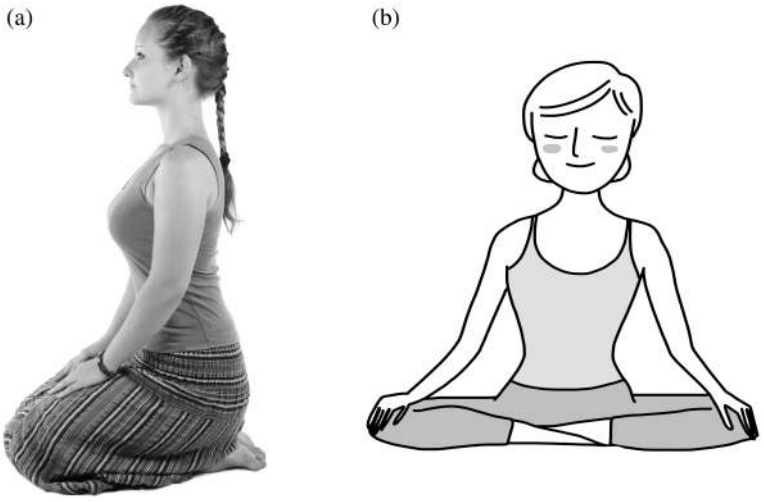


Figure 2.5 Sitting on the floor: (a) *vajrasana* (kneeling pose); (b) *sukhasana* (easy pose).

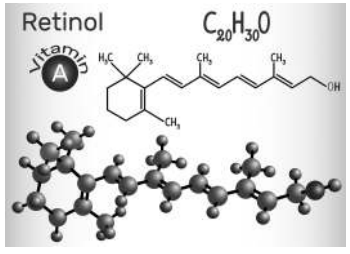
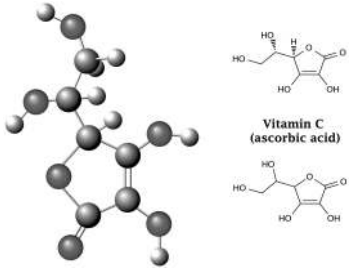
The pelvis and legs get more open, flexible and the central muscles get strengthened while the lower regions of the legs are extended additionally. When the person sits to consume food in a suitable position, all digestive juices start releasing in the stomach, which then prepares the stomach for dealing with the food. The vagus nerve (the principal nerve in the human body that transmits the signal from the gastric system to the nervous system) starts working appropriately as soon as the person begins eating; sitting on the floor improves the nerve's functions and transfers all signals efficiently (de Brito et al., 2014; MacDonald, 2010; Sampath, 2015).

Contemporary Nutritional Approaches and How Deficiency of Certain Nutrients Can Affect the Body

Though nutrition and food have been researched for hundreds of years, the contemporary science of nutrition is astonishingly new. The first vitamin was separated and chemically described in 1926. In contrast, the study of the role of nutrients in noninfectious multifaceted disorders such as diabetes, cancers, obesity and cardiovascular diseases is even more new, speeding up over the past 20 or 30 years and particularly after 2000. The initial part of the 20th century observed the synthesis and recognition of lots of the identified essential minerals and vitamins. Moreover, their consumption prevents and manages the disorders associated with deficiency of nutrients, such as xerophthalmia (deficiency of vitamin A), scurvy (deficiency of vitamin C), pellagra (deficiency of vitamin B3), nutritional anaemia, rickets (deficiency of vitamin D) and beriberi (deficiency of vitamin B1 or thiamine). In 1913, Casimir Funk brought about the idea of a 'vital amine' in food items, starting from the finding that the unprocessed rice hulls prevented chicken from a thiamine deficiency–like disease (Mozaffarian et al., 2018). This vitamin or 'vital amine' was initially separated in 1926 and termed thiamine, and ultimately developed in 1936 as vitamin B1. Meanwhile, vitamin C was separated and ultimately reported for the first time in 1932 to prevent scurvy (Schultz, 2002) after James Lind (surgeon of the ship) experimented with lemons for managing scurvy in sailors (Bartholomew, 2002). Near the middle of the 20th century, all chief vitamins had been separated and developed. Their recognition in human and animal studies verified the nutritional basis of severe deficiency disorders; it primarily gave rise to dietary approaches to manage pernicious anaemia, beriberi, rickets, scurvy, pellagra and other disorders of nutrient deficiency. The novel science for disease development caused by deficiency of particular nutrients also gave rise to the fortification of some foods and micronutrients, such as iron and vitamin B3 in bread and wheat flour and iodine in salt (Mozaffarian et al., 2018). These tactics were established to be efficient in inhibiting the prevalence of many deficiency ailments, including anaemia, goitre, rickets and xerophthalmia. All around the globe, foods have since been fortified with vitamins, iron, calcium and phosphorus, based on the constitution of important local food, since the increasing burden of noninfectious diseases started to be identified, giving a new direction for research (Fletcher et al., 2004; Mozaffarian et al., 2018; Tazhibayev et al., 2008) (Table 2.1).

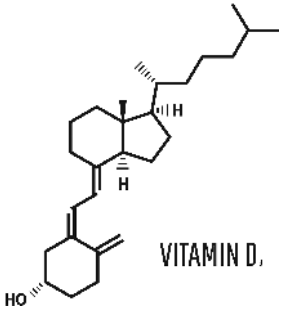
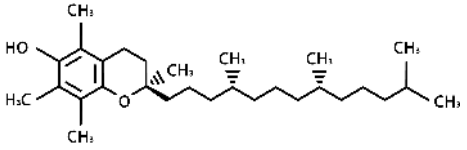
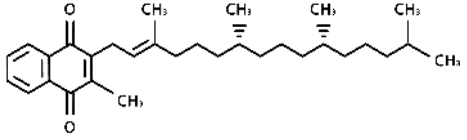
Two categories received special attention: sugar and dietary fat (Mozaffarian et al., 2018). The researchers Ancel Keys, Mark Hegsted and Frederick Stare, among others, contributed to the common perception that fat was a major cause of heart disease through early ecological research and tiny, short-term treatments. Increased intake of sugar was also linked to hypertriglyceridemia, dental cavities, cancer and cardiovascular diseases, according to research by John Yudkin as well as others. The fat concentration eventually gained policy and scientific recognition, as evidenced by the 1977 committee report of the US Senate, i.e. *Dietary Goals for the U S*, which advised low cholesterol and low-fat diets for everyone. The United States National Academy of Food and Nutrition Sciences Board analysed the data in 1980 and determined that there was a lack of evidence to limit consumption of dietary cholesterol, saturated fat and total fat in the general population (Mozaffarian et al., 2018). Malnutrition experts also argued over the respective importance of proteins and total calories in disorders such as kwashiorkor and marasmus, also known as

Table 2.1 Source of Vitamins and the Outcomes Caused by Deficiency of Certain Vitamins

Name of vitamins	*Chemical structure*	*Insufficiency can cause*	*Food sources*	*References*
Vitamin A		Visual impairment, dry eye syndrome, keratomalacia, Bitot's spots, infections of pulmonary and intestinal tract, follicular hyperkeratosis and growth retardation	Cod liver oil, carrots, papaya, yellow fruits, meat, cereals, vegetables, spinach, fish, pumpkin, green leafy vegetables, pulses and green mango	(Abrha et al., 2016; Structural Genomics Consortium et al., 2008)
Vitamin C		Scurvy: symptoms include bleeding, swelling of joints and muscular pain	Grapefruits, lemons, green leafy vegetables, oranges and beef liver	(Ferraro et al., 2016; Luiz Gomes et al., 2018; Sorice et al., 2014)

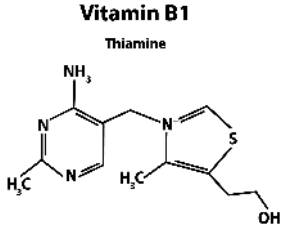
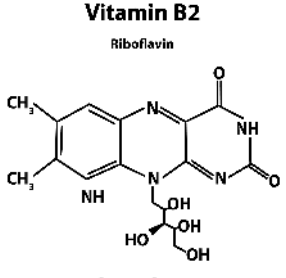
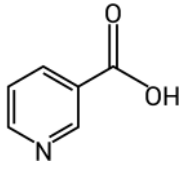
(*Continued*)

Table 2.1 (Continued) Source of Vitamins and the Outcomes Caused by Deficiency of Certain Vitamins

Name of vitamins	*Chemical structure*	*Insufficiency can cause*	*Food sources*	*References*
Vitamin D		Rickets, osteomalacia, impairment in development of bones and proneness to the risk of fractures	Eggs, fortified foods, fish liver oil, sunlight exposure, cheese, milk, butter and liver	(Christakos et al., 2016; Găman et al., 2020; Kennel et al., 2010; Nair & Maseeh, 2012)
Vitamin E	 Vitamin E $C_{29}H_{50}O_2$	Habitual abortions, ataxia, cystic fibrosis, increased RBCs hemolysis, abetalipoproteinemia and macrocytic anaemia in infants	Green leafy vegetables, nuts, eggs, wheat germ oil, cereals and milk	(Akram et al., 2020; Birringer et al., 2019; Schmölz et al., 2018)
Vitamin K	 Vitamin K $C_{31}H_{46}O_2$	Prolonged clotting time, development of haemorrhagic disorder in newborns	Liver, egg yolk, lettuce, soybean oil, green leafy vegetables and cabbage	(Reddy & Jialal, 2021)

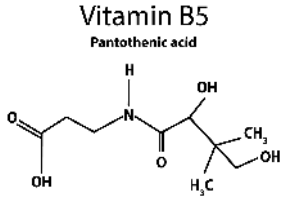
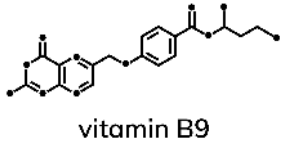
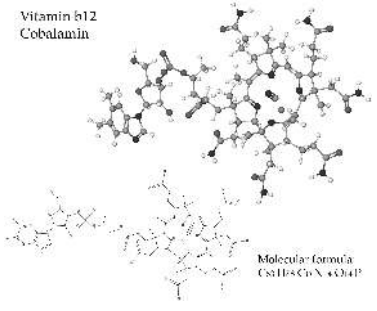
(*Continued*)

Table 2.1 (Continued) Source of Vitamins and the Outcomes Caused by Deficiency of Certain Vitamins

Name of vitamins	*Chemical structure*	*Insufficiency can cause*	*Food sources*	*References*
Vitamin B1 (thiamine)		Beriberi	Poultry, potatoes, eggs, beans, nuts, cereals, wheat germs, pork, beets, green peas, lentils and meat	(Romagnoli et al., 2012; Wiley & Gupta, 2021)
Vitamin B2 (riboflavin)		Ariboflavinosis	Liver, milk, eggs, oats and green vegetables	(Henriques et al., 2010)
Vitamin B3 (niacin)		Pellagra	Meat, cereals and yeast extracts	(Ronsein et al., 2016)

(*Continued*)

Table 2.1 (Continued) Source of Vitamins and the Outcomes Caused by Deficiency of Certain Vitamins

Name of vitamins	*Chemical structure*	*Insufficiency can cause*	*Food sources*	*References*
Vitamin B5 (pantothenic acid)		Skin disorders, enteritis and adrenal inadequacy, numbness and pain, mental depression and irritability	Dairy products, fish and sunflower seeds	(Combet & Buckton, 2015; Lykstad & Sharma, 2021)
Vitamin B9 (folic acid)		Neural–tube defects in foetus, megaloblastic anaemia and mouth sores	Grains, green leafy vegetables, orange juice, liver and fruits	(Combet & Buckton, 2015; Marcus, 2013)
Vitamin B12 (cyanocobalamin)		Neurological deficits, megaloblastic anaemia, neuropsychiatric	Shellfish, egg, milk, meat, liver	(Akram et al., 2020; Lykstad & Sharma, 2021)

'deficiency diseases of protein and calories' in children and infants (Carpenter, 1994; FAO/WHO/UNU, 1985). The 'protein gap' notion has resulted in the substantial commercial development of formulae enriched in proteins and supplemental foods for underdeveloped countries. At the same time, other researchers agreed upon the primary function of calorie deficiency and accepted that protein-fortified foods and formulas should not be used to substitute breast milk. In 1966, according to one of the renowned researchers, 'Years of efforts and millions of dollars … into inventing these protein-rich foods would have been spent better on measures to sustain the breastfeeding practice … being discontinued globally' (Carpenter, 1994). According to the guidelines about diet in 1980, the huge emphasis was upon nutrients: avoiding excessive cholesterol, excessive sugar, saturated fat or great amount of fat and excessive sodium, while consuming foods with sufficient fibre and starch; moreover, the international guidelines were identically focused on nutrients (Mozaffarian et al., 2018; World Health Organization, 2003).

On the other hand, vegetarianism is gaining popularity in developed countries as well. Though vegetarianism is not generally practised, it is enormously the diet of choice in the holistic environment, as a meatless diet is thought to be beneficial to the soul, body and mind. Meat was consumed during the Vedic period, and the Caraka Samhita does not certainly recommend vegetarianism. The Caraka Samhita emphasises that no single food should be consumed in excess and advises several foods for specific physiological aspects. It mentions a variety of meats, such as cow and camel, as a contribution to mitigating the effects of various disorders, such as persistent piles, and as being 'good for individuals who exercise daily and have great digestive powers' (Jacobs, 2018).

Importance of Polyunsaturated Fatty Acids and Other Bioactive Constituents in Preventing Cardiovascular Diseases

Currently, disorders of the cardiovascular system are one of the leading causes of mortality, classifying first all around the globe. In accordance with the World Health Organization, 17.5 million individuals die from cardiovascular diseases annually, which is determined as 31% of all fatalities globally (World Health Organization, 2021). Around 6.7 million people passed away from stroke and 7.4 million people from coronary artery disease (Institute of Medicine [US] Committee on Diet and Health, 1992; Jamee Shahwan et al., 2019). Cardiovascular disease's risk factors include hyperlipidemia, sedentary lifestyle, obesity, diabetes, stress, hypertension, malnutrition, genetic predisposition and consumption of alcohol and tobacco (Holvoet, 2012). In accordance with the clinical and preclinical research studies, an appropriate diet has a protective effect on the health of the cardiac system. Cardiovascular disorders can be prevented by taking a diet loaded with vegetables, low-fat milk products and fruits while low in sweets, fats, red meat and sugary beverages, restricting the intake of salt and soda, and adequate consumption of Mg2+, K+, Ca2+, ω-3 fatty acids and vitamin C. Bioactive molecules from plant-based food products with several chemical structures, such as peptides, vitamins, oligosaccharides, fatty acids and polyphenolic constituents, have protective effects on the cardiac system (Chen et al., 2005; Sharifi-Rad et al., 2020). Intake of wholegrain food is related to decreased risk of cardiovascular disease since wholegrain food is comprised of minerals, phytoestrogens, fibre, phenolic constituents and vitamins. These

compounds have favourable health activities such as inhibiting blood pressure and serum lipid levels, mitigation of inflammation and oxidative stress and improving the functions of the endothelium (He et al., 2010). Amid several plant-originated bioactive constituents, polyphenols are among the most significant group of organic anti-inflammatory, antioxidant and cardioprotective agents established in foods of humans, including seeds, herbs, vegetables, fruits and grains (Salehi et al., 2019).

Polyphenols can make the health of the cardiovascular system better by inhibiting vascular inflammation, restricting oxidation of LDL (low-density lipoprotein), reducing aggregation of platelets, regulating the processes of apoptosis and making the lipid profile better (Vuong, 2017). Many studies have proposed that dark chocolates, citrus fruits and products loaded with cocoa consist of high flavonoid concentrations associated with reduction of risk for cardiovascular disorders (Cicero & Colletti, 2017; Duthie et al., 2000). Similarly, *Camellia sinensis* and its extracts have great levels of EGCG (epigallocatechin gallate) and flavan-3-ol molecules, which are among significant antioxidants for cardiovascular systems. Black tea has strong antioxidant properties but is lower than green tea extract. Extracts of both teas assist in inhibiting blood pressure, which can have a positive impact on the risk profile of the cardiovascular system (Cicero & Colletti, 2017).

ω-3 fatty acids, including eicosatetraenoic acid and ω-3 docosahexaenoic acid, are accountable for normal brain development, decreased risk of cardiovascular disease and optimal vision (Abedi & Sahari, 2014). Docosahexaenoic acid and eicosapentaenoic acid have cardioprotective, anti-inflammatory, antithrombotic and anti-arrhythmic properties. They also cause a reduction in blood pressure, inhibit the atherosclerotic plaque growth and provide strength to the endothelial function (Ander et al., 2003), so these molecules appear to be promising molecules along with anti-ageing, antioxidant, anti-arthritic, antihypertensive and antidepressive effects (Siriwardhana et al., 2012).

In the field of medicine, ω-3 fatty acids are distinguished by multidirectional activities in man: they demonstrate antihypertensive and anticoagulant properties, control metabolism of lipids and provide support for the functioning of eyes and central nervous system; ω-3 fatty acids also give a broad scope of anti-inflammatory activities, which makes them effective agents for utilisation in patients with several conditions or disorders associated with inflammation. Many researchers have also advised that ω-3 fatty acids may have a considerable role in preventing different kinds of cancer. Numerous studies on stroke models have demonstrated that ω-3 fatty acids are capable of protecting against the ischemic injury of the brain (Sharifi-Rad et al., 2020) (Figure 2.6).

Weight Management and Disease Prevention

Since 1975, obesity has approximately tripled globally. More than 1.9 billion adults aged 18 and over were overweight in 2016. Among these, more than 650 million of that population were obese. Obesity and overweight are described as unhealthy or excessive accumulation of fat that can harm one's health and are associated with more fatalities globally than are caused by being underweight. Noninfectious disorders such as disorders of the cardiovascular system (mostly stroke and cardiac disease), which were the leading death cause in 2012, moreover musculoskeletal problems, diabetes and various malignancies are all linked to a high BMI (including

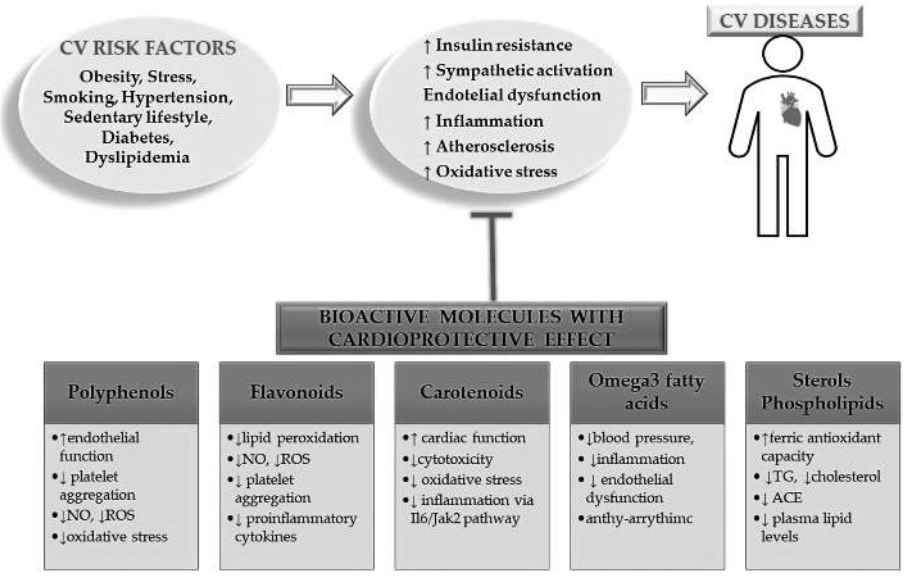


Figure 2.6 Overview of CV risk factors, the pathophysiology of CV diseases and the cardioprotective mechanisms and effects of plant-food-derived bioactive compounds, including ω-3 fatty acids. (Source: illustration acquired from 'Diet, Lifestyle and Cardiovascular Diseases: Linking Pathophysiology to Cardioprotective Effects of Natural Bioactive Compounds' by J. Sharifi et al. (2020) *Int J Environ Res Public Health*.)

carcinoma of colon, endometrium, prostate, breast, liver, ovaries, kidneys and gallbladder). (Harvard Public Health School; WHO, 2021b). In accordance with the rising clinical data, increasing incidence of metabolic syndromes, such as dyslipidemia, hyperglycemia and inflammation, have been linked to a diet that is rich in calories and have an abundant quantity of carbohydrates and saturated fat but low quantities of protein (Hou et al., 2019). Obesity and overweight, as well as the disorders associated with them, are mostly preventable. Risk-reduction and prevention initiatives, including dietary guidelines, are critical to alleviating this burden.

Besides dietary guidelines, a focus on health-maintaining foods that integrate with current dietary methods is critical for preventing and managing a variety of chronic disorders (Hall et al., 2017). Several international health organisations have advised a range of plant-based food products, triggering a need for major diet adjustments to promote health and prevent chronic disorders (Hou et al., 2019). After cereals, legumes are regarded as the second most significant food crop for humans. However, seeds of legumes are an important part of the diet in humans, in comparison to cereals, since they are a great source of minerals, proteins, vitamins and bioactive constituents and are considered as 'meat for poor man' (Hall et al., 2017; Singh et al., 2017). The dietary guidelines of the recent era recommend a range of healthy dietary habits that include plenty of vegetables, fruits, whole grains, seeds and nuts, along with vegetable oils, yoghurt and seafood, while on the other hand limiting the consumption of processed, preserved and red meats, added sugars, refined grains and starch. Vegetables and fruits such as cruciferous vegetables, berries, citrus

fruits and green leafy vegetables are loaded with several vital nutrients and other bioactive constituents that can give protection against a number of chronic disorders (Al-Dashti et al., 2021).

Health-Preserving Food and Drinks That Also Help in Boosting Immunity

The intricacy of associations between immunology and nutrition is extensive. A person's overall status of nutrition, the pattern of food consumption and state of nourishment influence the performance of the immune system; this influence can take place at the levels of the adaptive immune system, the microbiome, the function of the innate immune system and physical barriers such as intestinal mucosa and skin. It is now identified that signalling molecules and transcription factors control the inflammatory cascade and that a lot of chronic disorders are originated by impairment of inflammatory pathways, and by successively giving rise to chronic inflammation. The functional foods that have anti-inflammatory effects consist of several bioactive constituents and are more appropriate for the treatment of chronic ailments in contrast with agents that are pharmaceutical-based; because they are effective on various molecular targets, the perceived anti-inflammatory benefits of plant chemicals have been ascribed to the following action mechanisms: (1) undeviating antioxidant activity or escalation in the appearance of antioxidant proteins; (2) diminishing stress signalling of the endoplasmic reticulum; (3) impeding the pro-inflammatory cytokines; (4) obstructing the transcription components associated with metabolic disorders; (5) elicitation of expression in metabolic genes; and (6) stimulation of transcription elements that antagonise inflammation (Iwu, 2017) (Figure 2.7).

Pecel

This is a traditional Indonesian dish and has a blend of boiled vegetables, predominantly sprout, carrot and spinach, which is provided with peanut sauce. At the same time, the peanut sauce is mixed generally with brown sugar, salt, tamarind, garlic paste, lime leaves and chilli. Traditionally, this dish is served on leaves of banana or *ingke* (traditional plate of Indonesia) and blended with rice and other side dishes such as prawns or fish. Pecel is loaded with several bioactive constituents, including iron, vitamin E, genistein, folic acid, lutein and β-carotene (Harmayani et al., 2019; Rizki, 2013) (Figure 2.8).

Khichdi

The word khichdi originated from the Sanskrit word '*khicca*', a food item from the Indian subcontinent prepared with a blend of lentils and rice, which is rich in healthful goodness and is gluten-free and easy to digest. Khichdi is a porridge usually prepared with salt instead of sugar, owing to the feasibility of being capable of cooking in only one stewing pot (Khandekar et al., 2020). An intake of mung beans (*Vigna radiata*) daily is advised in the *Charaka Samhita*. The moong daal or mung bean has a slightly astringent and sweet taste; it has cold and

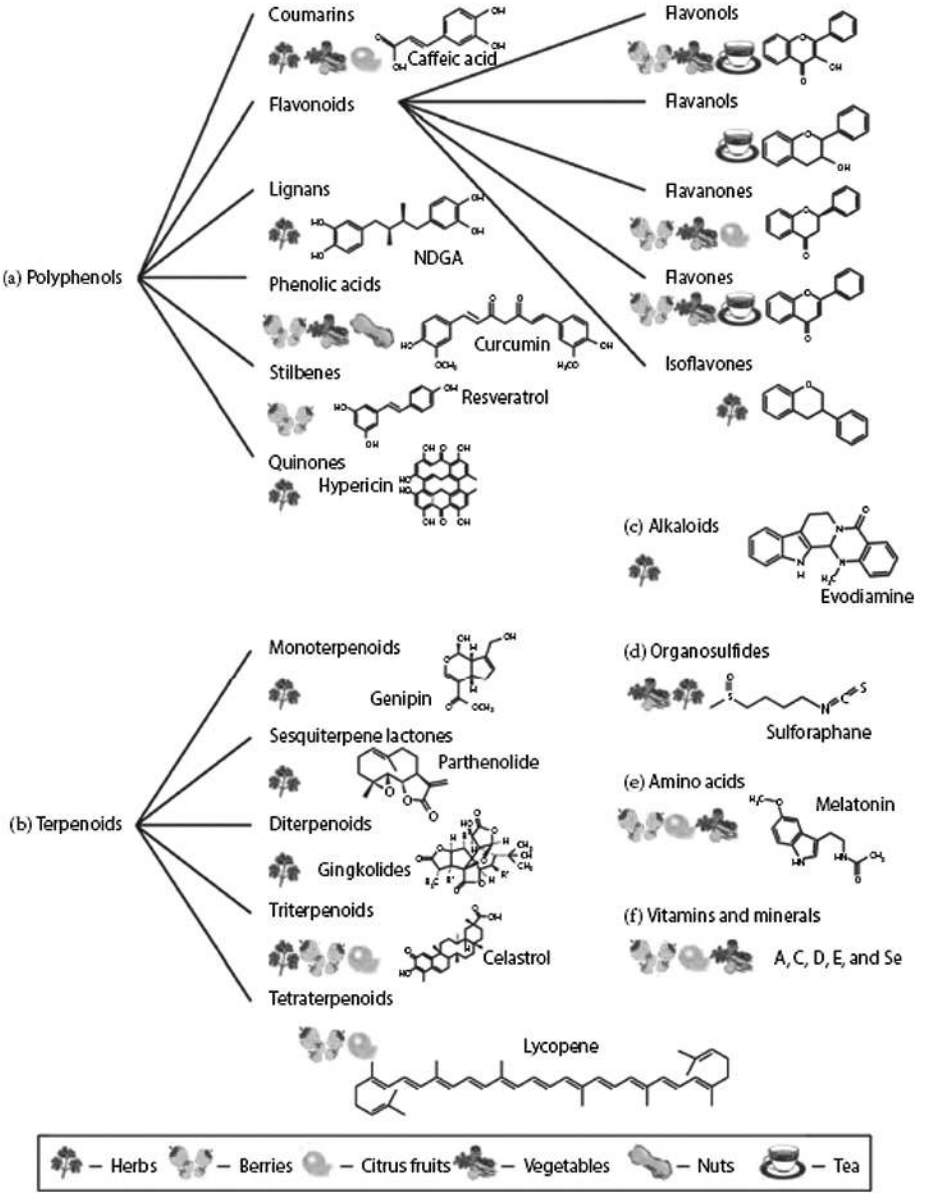


Figure 2.7 Bioactive compounds found in common food sources. Each chemical category is depicted with an example and linked to potential dietary sources. (Source: illustration acquired from Chapter 6, 'Effect of Phytonutrients on Chronic Inflammatory Diseases and Aging' in: *Food and Medicine: Functional Food Plants of Africa* (2017), CRC Press.)

Figure 2.8 Traditional Indonesian pecel prepared with boiled vegetables and peanut sauce.

Figure 2.9 Khichdi.

dry properties and balances the *pitta* and *kapha doshas* (body humours). In the Ayurvedic text of *Yogratnakara*, the therapeutic properties of mung bean (*Vigna radiata*) give nutrition to the body tissues. Its cold properties provide smoothness to the skin, inhibit heartburn symptoms, decrease rashes and strengthen the body. Khichdi prepared from mung bean is a wholesome meal loaded with nutrients and is beneficial for the stomach. It also helps reduce the excessive heat of the body, improves digestion, decreases hyperacidity and is useful for diarrhoea, indigestion and any prolonged illness (Āś ā Kumārī & Tivārī, 2010; Mehta, 2017; Sharma, 2007) (Figure 2.9).

Figure 2.10 Coconut water.

Coconut Water

Coconut water is a somewhat sweet liquid drink with a sharp, nutty flavour acquired from the endosperm of *Cocos nucifera* L. Coconut water is low in fats and calories. It works as a natural sport or energy drink because it is rich in antioxidants, amino acids, growth-promoting factors, sugars, minerals (magnesium, potassium, sodium chloride and phosphorus), vitamins and proteins (Yong et al., 2009). Coconut water inhibits cholesterol, helps blood sugar levels and prevents kidney stones by decreasing stone and crystal synthesis (Siriphanich et al., 2011) (Figure 2.10).

Sayur Tempe Lombok Ijo

This is a soup prepared by using coconut milk, tempe and green chilli; this dish has been derived from the Yogyakarta Special Region, Indonesia. Tempe, predominantly prepared from the soybean (fermented), was traditionally discovered as the protein substitute with minimum cost and got famous for regular consumption in Indonesia because of its nutritional values and taste. The most beneficial effect of this soup is primarily because of the tempe, which consists of vitamin B12, antioxidants, proteins, polysaccharides, vitamins, plant chemicals and other bioactive constituents (Astuti et al., 2000). Tempe prevents cardiovascular disorders, improves the health of bowel, improves the health of menopausal women and protects from malignancies such as breast carcinoma. A reduction in oligosaccharides, particularly raffinose and its content, throughout the processing of tempe eradicates the problems of flatulence usually noticed when taking soybeans. Tempe has constructive effects on levels of cholesterol and histopathological modifications in the arteries and hepatic system. Its compounds decrease the enzyme, which is accountable for cholesterol biosynthesis and prevents LDL (low-density lipoprotein) oxidation, hence inhibiting the synthesis of arterial plaques. The glucolipids in tempe decrease the tumour cell proliferation in rodents (Harmayani et al., 2019) (Figure 2.11).

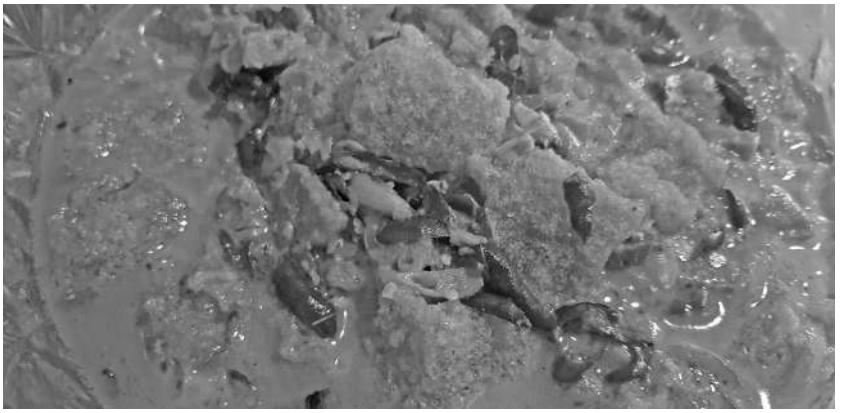


Figure 2.11 Sayur tempe lombok ijo.

Idli

Idli is prepared by a batter of *Vigna mungo* and rice by cooking it on steam (Agarwal & Bhasin, 2002). It is a fermented white-coloured round, spongy and small edible product. Using pulses with rice is compulsory for enhancing the microflora required for effective fermentation. *Vigna mungo* L is naturally the chief constituent with microflora fermentation ability and works as the fermentation substrate for the batter. Buttermilk or yoghurt is also used as a microorganisms source (Radhakrishnamurty et al., 1961). *Vigna mungo* (black gram) and rice are utilised in the proportion of 1:2 during batter preparation. Idli batter fermentation improves protein efficiency and nutritional values (Reddy et al., 1982). The chief microbes included in the leavening method of idli are heterofermentative *Lactobacillus mesenteroides* and lactic acid bacteria, while the acidity of the mixture is controlled by homofermentative *Streptococcus faecalis* (Mukherjee et al., 1965). Moreover, probiotic microbes such as *Lactobacillus lactis* and *Lactobacillus plantarum* are also established in the batter of idli. These microbes can synthesise beta-glucosidase enzyme and vitamin B12, which promotes health and increases the activity of probiotics (Iyer et al., 2013) (Figure 2.12).

Kang Liang

It is a traditional Thai soup recipe prepared with a combination of herbs and vegetables with high fibre and minimum calories. Kang liang is a source of minerals, vitamins and plant chemicals such as flavonoids and β-carotene. It is prepared as a curry with herbs and different vegetables. It is a bit salty because of the curry paste, spicy because of pepper, a little sweet because of vegetables and has a good smell of basil leaves and shallots. The chief constituents are *Ocimum basilicum* (basil or tulsi leaves), shrimp paste, black pepper, shallot, *Capsicum frutescens* (Thai chilli) and dried pulverised shrimp. Other constituents are water, pumpkin, baby corn, winter melon, ivy gourd, fish sauce, fresh vegetables and angled luffa. This soup is loaded with flavonoid content and β-carotene, which may inhibit the pathological expression of an early cancerous lesion in the colon of rodents by 50% and invigorate the

Figure 2.12 Idli (famous south Indian breakfast).

Figure 2.13 Thai soup kang liang.

functioning of detoxification enzymes in the liver of the rats. Edible Thai herbs have been documented for their anti-carcinogenic and anti-mutagenic properties in vivo and in vitro (Kangsadalampai & Pratheepachitti, 2008) (Figure 2.13).

Zamzam

People from numerous beliefs and religions have consumed 'holy water' for management and other religious practices from prehistoric times. Many Muslims have a firm belief that the water from the well of Zamzam is blessed sacredly, capable of

gratifying both thirst and hunger, as well as managing disease. The pH signifies that the water of Zamzam is alkaline, which could be the reason for its healing properties. Numerous studies have described the mechanism by which water with alkalinity encourages healing. For instance, Kellas and Dworkin (1996) mention that consuming alkaline water plays a significant role in eliminating other toxins and mercury from the body. If the body has more acidic content in it, the more it grips onto the heavy metals, while a significant amount of heavy metals in the body produces great oxidative stress that makes the body acidic. Therefore, alkaline water has been consumed for making the density of bone better and for healing purposes (Wynn et al., 2009); regulating the gastric functions (Bertoni et al., 2002); enhancing the capability of the body for aerobic actions; and flushing out the acidic content and toxins (Shomar, 2012) (Figure 2.14).

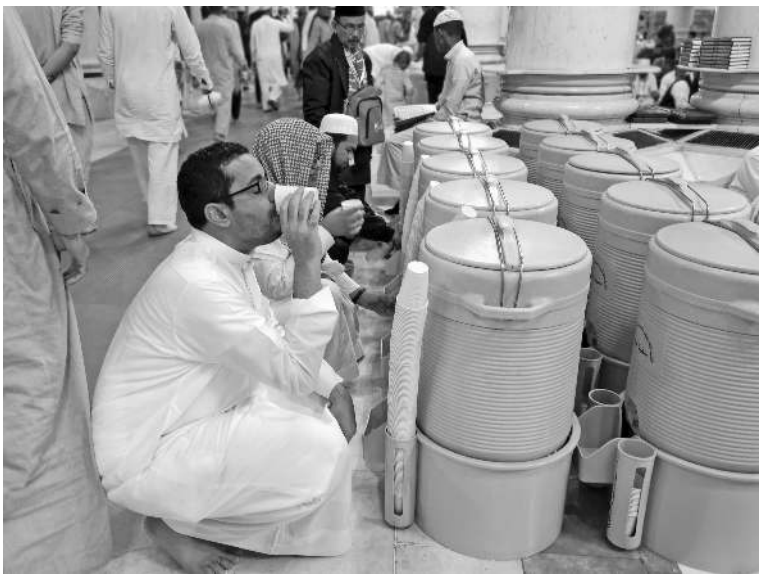


Figure 2.14 Zamzam water.

*Bael (*Aegle Marmelos*) Juice*

It is consumed in traditional Tibetan, Chinese, Ayurveda, Siddha and Unani medicines. Ancient texts such as the *Sushruta Samhita*, *Rigveda*, *Charak Samhita*, *Atharvaveda*, Avicenna's *Canon of Medicine* and *Yajurveda* also discuss the consumption of different plants and foods for the management of several health issues. Bael is advised for many disorders such as obesity, piles, jaundice, gynaecological disorders, oedema, vomiting, urinary problems, pediatric diseases and as refreshing fruit. Other ingredients used with bael to prepare its juice include water, salt and sugar. Powder of desiccated fruit pulp is consumed as antipyretic, stimulant and antiscorbutic (Patkar et al., 2012). The therapeutic activities of *Aegle marmelos* fruit are antidepressant, adaptogenic, insecticidal, antioxidant, antibacterial, antipyretic, antihistaminic, hepatoprotective, anxiolytic, anti-inflammatory, wound healing,

Figure 2.15 Bael juice.

immunomodulatory, analgesic, hypoglycaemic, cardiotonic, wound healing and anti-stress. It also has an impact on testicular diseases and myocardial infarction. The fruit of bael is stated to have flavonoids, alkaloids, terpenoids, steroids, inulin, carbohydrates, lignin, proteins, cardiac glycosides, steroids and phenolic constituents (Harmayani et al., 2019) (Figure 2.15).

Talbina

Talbina is an Arabic dish made up of a combination of honey, barley and milk. The Prophet Muhammad PBUH suggested talbina for alleviating sorrows of the heart, for sadness and depression. It has a promising therapeutic and nutritional impact on health. Talbina is a rich source of several nutrients and bioactive components. Daily intake of talbina assists in preserving the health of the gastrointestinal tract and works as an antioxidant, antidiabetic, antidepressive, anti-inflammatory and antihypercholesterolemic. Furthermore, it is most efficient in removing toxins and providing nutrients to cells of the human body. According to the studies carried out for depression, it is associated with vitamin B deficiency (Mikkelsen et al., 2016). The talbina is a rich vitamin B source that is beneficial for the nervous system for making several chemicals that eventually have an impact upon psychological manifestation and mood in humans. So there is a rationale why Prophet Muhammad PBUH stated that talbina takes away sorrows and grief, as the human body can't store vitamin B, so it must be consumed daily. It is verified from several scientific studies that barley and its products assist in the prevention of cardiovascular disorders (Afzaal et al., 2021). Research has confirmed that talbina makes the mood better and inhibits depression (Murakami & Sasaki, 2010). Talbina consists of bioactive constituents that have immunomodulatory and antioxidant properties and are associated with the prevention of cancer (Guilloteau et al., 2010) (Figure 2.16).

Figure 2.16 Talbina.

Mohi

It is the native drink of Nepal with great nutritional value. Mohi is a liquid of fermented milk, a by-product of yoghurt. Its taste is sour because of the lactic acid found in yoghurt. It is taken as a cold drink during summertime, and it also suppresses tiredness and provides freshness. While sugar or any sweetening agent can be mixed with it to enhance its taste, mohi is extensively advised as a beneficial remedy for certain diseases such as dysfunctions of spleen and liver, piles, jaundice and diarrhoea as it also consists of probiotics. The fat content of mohi is far lesser in contrast with curd or milk since most of the fat is eliminated during churning. Around 250 ml or one cup of mohi consists of 2.2 grams of fat and 99 calories. It also consists of phosphorus, calcium, potassium and vitamins (Tamang, 2019) (Figure 2.17).

Figure 2.17 Traditional Nepali beverage, mohi.

Conclusion

Nutrition and diet have the potential to improve any ailment and to prevent a considerable number of diseases. Though physicians should provide authentic advice to patients, further systematic studies of nutritional and diet patterns and/or individual nutrients' impact on the function of the immune system, epigenetic and microbiological modifications have to be executed to understand the part of nutrition in causation and management of diseases altogether. Once people start to understand the satisfaction of consuming food should be associated with the outcomes of food, they can then emphasise the efficient execution of specific dietary habits and healthy ways of consuming food.

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Chapter 3

Fasting

A Spiritual and Physical Cleansing for Strengthening the Human Immune System

Introduction

Fasting in humans is observed by consuming nothing or minimal quantities of beverages and food for durations that generally vary from 12 hours to around 21 days. Numerous religious categories integrate fasting periods into their traditions, including Muslims, who used to fast in the holy month of Ramadan from daybreak to dusk. Moreover, Jews, Hindus, Christians and Buddhists commonly fast on selected weekdays or calendar years (Longo & Mattson, 2014). In several clinical setups, patients are now watched by doctors while observing water fast or receiving extremely low calories (< 200 kcal per day), continuing from seven days or greater for prevention and management of diseases and weight management. Fasting is distinctive from calorie restriction, among which the regular calorie consumption is persistently decreased by 20–40%; however, the frequency of meals has remained the same. Alternatively, starvation is a persistent nutritional inadequacy that is generally applied as a replacement for the word 'fasting', especially in lower eukaryotes; however, it is also used to interpret intense forms of fasting, which can lead to deterioration of health and ultimately death. Fasting causes ketogenesis, encouraging strong modifications in cellular processes and metabolic pathways, i.e. autophagy, lipolysis and stress resistance, and can have applications in the medical field that, in a number of cases, are as efficient as those of recommended medicines, for instance, diminishing of seizures and related brain destruction and improvement of rheumatoid arthritis (Bruce-Keller et al., 1999; Hartman et al., 2013; Müller et al., 2001).

Fasting is described as a total or partial abstinence from all kinds of foods or a specified refrainment from forbidden foods. As a prospective non-medicinal

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intervention for improving the quality of health and enhancing longevity, fasting has been the topic of several scientific studies.

On the other hand, calorie restriction has been shown to enhance longevity and ameliorate health in various groups of species, including zebrafish, spiders, dogs, rodents, fruit flies, rotifers, nematodes and non-human primates, i.e. monkeys, apes etc. (Spindler, 2010). Moreover, calorie restriction seems to procrastinate the onset of the following ailments: pulmonary disorders, atherosclerosis, neurodegenerative disorders, autoimmune disorders, kidney diseases, cancer, cardiomyopathies and diabetes (Imai, 2009; Vaquero & Reinberg, 2009). Concerning the health of the cardiovascular system, the following modifications have been observed following an administration of calories restriction; i.e. reduction in resting blood pressure and heart rate, enhancement in the function of the left ventricle, post-exercise recuperation of both blood pressure and heart rate and flow-moderated vasodilatation (Mattson & Wan, 2005).

With reference to glucoregulatory health, calorie restriction has been revealed to inhibit the levels of insulin and fasting glucose, enhance insulin sensitivity, reduce the percentage of body fat and inhibit diabetes incidence (Fontana & Klein, 2007; Mattson & Wan, 2005). Alternate-day fasting comprises of 24 hours alternating fasting periods in which throughout the 'feeding period' the fasting person may eat ad libitum; whereas during 'fasting period' consumption of food is absolutely halted or restricted, although consuming water is permitted ad libitum throughout the fasting and feasting durations. Experimental trials for alternate-day fasting have documented lengthened lifespan in animals (Spindler, 2010) as well as the absolute prevention of numerous diseases' development, including diabetes, renal disorders, cardiovascular disorders and cancers (Varady & Hellerstein, 2007; Mattson & Wan, 2005). Alternate-day fasting has been observed to bring about the following useful modifications in the health of the cardiovascular system: reduced blood pressure and heart rate, enhanced variability of heart rate and impaired post-infarct heart failure (Ahmet et al., 2005; Mager et al., 2006; Mattson & Wan, 2005). Concerning glucomodulatory health, alternate-day fasting may have gender-specific effects. For example, ADF enhanced the sensitivity of insulin in men; however, this variable had no impact on women.

Moreover, tolerance of glucose was unaffected in men partaking in a regimen of alternate-day fasting; however, women partaking in the identical process encountered impaired tolerance of glucose (Varady & Hellerstein, 2007). Dietary restriction is inhibition of one or more constituents of dietary consumption (generally macronutrients) with the lowest to almost no reduction in consumption of total kcal. A research study proposes that neither restriction of carbohydrates nor restriction of fat prolonged life (Ayala et al., 2007). Contrastingly, restriction of protein enhances maximum lifespan by approximately 20% (Pamplona & Barja, 2006), and this life extension may be merely because of the inhibition of methionine (amino acid) (Caro et al., 2009).

There are substantial medicinal benefits of fasting, and even doctors of contemporary medicine advise their patients to fast for the management of metabolic diseases, obesity and hormonal fluctuations so that the patient's body gets balanced. The researchers also identify the importance of fasting in oncology and how calories and specific nutrient restrictions may help in abnormal cellular growth. This chapter will discuss the introduction of fasting, the historical importance of fasting in different religions, physiological changes in tissues and systems of the

body of a fasting person, what a Daniel fast is and what its benefits are, potential benefits of intermittent fasting, metabolic effects of fasting, effects of fasting on various hormones, how fasting enhances expectancy of life and other health benefits of fasting.

Religious Importance of Fasting

While religious fasting is manifested fundamentally for spiritual reasons, it also has the capability to influence the physical health of an individual. Consequently, in recent times, the health benefits of spiritual fasting have been the topic of scientific exploration, with a large number of research studies being carried out in the past 20 years. The following spiritual periods of fasting are discussed in this chapter: (1) fasting in the religion of Islam, (2) fasting in Judaism, (3) fasting in Hinduism, (4) fasting in Christianity including (i) Greek orthodox fasting and (ii) biblical-based Daniel fasting and (5) fasting in Buddhism. The reason for including these certain forms of spiritual fasting is that these are the most commonly discussed types, and numerous scholarly pieces of literature and books have also discussed these types (Trepanowski & Bloomer, 2010).

Religious or spiritual fasting also encourages other human qualities and moralities, for instance, gratefulness, honesty, generosity, forgiveness, altruism, self-discipline and patience. These distinctive features are necessary to be a supreme person and have a great impact on the chief facets of health, including psychological, physical, social and spiritual health (Massoud et al., 2019).

Fasting in the Religion of Islam

Globally every year, around 1.5 billion Muslims commemorate the holy month of Ramadan. Muslims religiously refrain from consuming any sort of liquid, food or any oral consumption, even smoking and medicines, from dawn to dusk (Aljaloud, 2020).

Ramadan fasting exhibits or covers some part of alternate fasting as in both cases, there are repeated durations of feeding and fasting. But the alternate-day fast includes oscillating periods of 24 hours of feeding and fasting while consuming water is also permitted (Persynaki et al., 2017). One of the meta-analyses states that people from East Asia showed more considerable loss of weight during Ramadan in contrast with individuals from west Asia (el Ati et al., 1995).

The holy Quran states about fasting:

> O you who have faith! Fasting is advised for you as it was advised for those prior to you so that you may become pious (Al-muttaqun). Fast for specified days; however, if any of you isn't feeling well or on a journey, the identical number of days should be compensated from other days. Moreover, the people for whom its difficult to fast such as elder persons, they have an option of either to fast or to give food to a needy or poor individual. Though whoever does righteousness by his own grant, it is more desirable and effective for him. So as you fast, it is superior for you if merely you recognize.
>
> (Abdel Haleem & Abdel Haleem, 2008; Al-Bukhari & Khan, 1997)

As a matter of fact, fasting during Ramadan is strongly encouraged and recommended as one of the pillars among five pillars of Islam (a fundamental of Muslim belief). For numerous practising Muslims, Ramadan is the holiest and most sanctified month, a period that is dedicated to improving or enhancing their spirituality in different ways, including Quran recitation, reading supplications and saying supplementary Salat. The basic teachings of Islam are principally originated from the Quran and the compendium of Hadith (sayings of Prophet Muhammad PBUH). Abu Hurayrah stated that the prophet Muhammad (peace and blessings be upon him) mentioned that:

> Every deed Adam's son does shall be magnified – a good deed by ten folds its worth, up to 700 folds. Allah states that: 'With the exclusion of fasting, which associates to me, and I reward it appropriately'. For the person who leaves his food and desire for my [Allah's] sake. 'There are two incidents of happiness for a person who is fasting: One is when he opens the fast, and another is when he meets his God, while the bad smell coming from the mouth of [a] fasting man is better in the view of Allah as compared to the Aroma of Musk.'
>
> (Alghafli et al., 2019)

Throughout Ramadan, there is a difference in the timings, frequency and constitution of the meals consumed (Meo & Hassan, 2015). But a regular pattern during Ramadan fasting is a single meal consumed prior to Suhoor (dawn), and another meal is consumed at Iftar (sunset) to break the fast, which is usually a sizeable meal. Since the frequency of meals taken is decreased from three to two meals regularly, the total amount and categories of each meal consumed are altered. This sequentially also influences nutrient and energy consumption (Al-Hourani & Atoum, 2007).

The modification in the constitution of meals consumed throughout Ramadan is anticipated to consist of more carbohydrate-loaded foods in the form of juices, fruits and dates (Meo & Hassan, 2015). One of the studies carried out on 366 Ghanaians established that during Ramadan, there is a rise in intake of vitamin A–loaded fruits and milk, while there was a minimum intake of legumes, nuts and dark leafy vegetables (Ali & Abizari, 2018).

On the contrary, another study of 160 Iranian participants found that there was an increased intake of vegetables and fruits throughout Ramadan; conversely, the intake of dairy products, meat and cereals reduced considerably. Thus, there are huge variations among different geographical locations and cultures in the modifications in eating patterns that happen during Ramadan. When contrasting the consumption of nutrients, a number of research studies have established an enhanced fat consumption during Ramadan fasting (Osman et al., 2020).

A cross-sectional research survey including 173 families in Saudi Arabia documented an increase in their weight during Ramadan; it was determined that around 40% of the participants ascribed their weight gain to the consumption of carbohydrates and fat-rich food in large amounts (Bakhotmah, 2011). But other research studies propose that there is a reduction in the consumption of fat during Ramadan fasting (Osman et al., 2020).

With respect to anthropometric factors, BMI may or may not reduce in reaction to fasting during the month of Ramadan; diverse findings exist concerning whether fasting during the month of Ramadan reduces or enhances the ratio of LDL/HDL cholesterol. Eventually, the ratio of total cholesterol/high-density lipoprotein

appears to reduce throughout Ramadan. Varying findings have been observed concerning other biochemical results throughout Ramadan fasting, including levels of blood glucose and triglyceride. Haematocrit or packed cell volume has been stated to either increase, decrease or remain the same. Most of the studies establish that levels of haemoglobin remain unchanged. Levels of transferrin have been stated to enhance during Ramadan (Trepanowski & Bloomer, 2010). Maughan et al. revealed that levels of serum ferritin reduced after almost 14 days of Ramadan fasting in participants assessed in the morning (Maughan et al., 2008); Chaouachi and colleagues (Chaouachi et al., 2009) stated that participants experienced a rise in levels of vitamin A in the blood and a reduction in levels of vitamin E in the blood during Ramadan (Trepanowski & Bloomer, 2010). Numerous research studies have verified that Islamic fasting not only has positive outcomes on bodily health but it also enhances mental health. Spiritual or religious fasting is linked with positive dedications, for instance, enhancement of religious wellbeing, reducing depression and advancing mental health. Furthermore, fasting in Islam has a great impact on health and wellbeing by means of eradicating negative feelings and emotions, i.e. greed, aggression and other offensive behaviours, while strengthening positive features, i.e. honesty (Massoud et al., 2019).

Fasting in Judaism

Fasting has significant importance in the traditional Jewish religion. In Judaism, fasting is described as 'complete abstinence from all kinds of drink and food'. A fast commences in the evening with sunset and extends uninterruptedly to the darkness of the succeeding day. Fasting may be an optional deed of penance or an obligatory act, according to the Jewish religious calendar (Bienstock, 2006).

In the Jewish religion, the 'day of expiation' or Yom Kippur is the holiest day of the year. It begins on the tenth day of the seventh month, in accordance with the Hebrew calendar, with limiting the intake of food and drink, even water. This day is commemorated for expiating the inequities or sins of the previous year to make oneself ready for one's 'return towards God', as refraining from the joy of food is meant to enhance the individual's capability to pay more attention to repentance. The people following the Jewish religion believe that on the celebration of the Jewish new year (Rosh Hashanah), God prepares judgements for everyone, and on the tenth day (Yom Kippur), judgement is concluded and secured (Venegas-Borsellino et al., 2018). Children below 13 years of age are not included in it, nor the ones whose health could be compromised by observing the fast (Grenader & Shavit, 2013). The duration of the fast is too brief to originate a considerable impact on health along with metabolic modifications.

However, restricting liquids for up to 25 hours has possible stress on physiological functions with prompt imbalances in homeostasis; on Yom Kippur, the fasting persons are permitted to consume 30 cc of food intermittently, if necessary. Fasting on the day of Yom Kippur is distinctive from fasting in other religions due to its absolute refrainment from water and food for up to 25 hours. Its possible instant hazardous effects are dehydration, headache and low blood glucose; however, because of its short period, sustainable or persistent influence on health is not likely to happen. However, limiting the intake of water can decrease the process of metabolism and may enhance physiological stress, possibly badly affecting the people living in hot

and dry regions. Other consequences such as headache and nausea can be observed in regular consumers of caffeine (Venegas-Borsellino et al., 2018).

Fasting in Hinduism

Fasting is also a fundamental part of Hinduism. There are various types of fasting for different goddesses and gods. People observe a variety of fasts based on their local traditions and individual beliefs. Religious fasting during festivals is also quite common such as the Navratri, Maha Shivaratri and the Kanta Shastiviratam. Fasting on the day of Shivaratri is one of the significant fasts dedicated to God Shiva. The individual who fasts with dedication, love and sincerity will be bestowed with the courteousness of God Shiva. On the holy day of Shivaratri, several people go on a diet of milk and fruits; a few amongst them do not even take a single drop of water during the whole night and day. The mythology of Hinduism expresses that if a believer observes the fast of Shivaratri with regulations, it will influence the standard of passionate activities and quality of inactivity. It will also assist in resolving the emotions of jealousy, lust and anger. Hindus used to fast on particular days, such as Purnima, Ekadasi and Pradosha. Specific weekdays are also considered for fasting depending upon the favourite god or goddess and on the individual's faith. For example, believers of God Shiva prefers to fast on Mondays, whereas believers of Lord Vishnu used to fast on Saturdays or Fridays (Natarajan et al., 2014).

What Does Ayurveda Say about Fasting?

Charaka Samhita, the ancient Ayurvedic compendium inscribed by Acharya Charaka (one of the principal contributors of Ayurveda), mentioned fasting with other approaches for managing a number of health problems; a few of its statements mentioning fasting are described next.

> In acute spreading inflammation (jalakagardabha), an individual should observe fasting, perform evacuation of the body, apply bloodletting and use the formulation of Emblica officinalis (Amalaki) and other ointments of cooling nature.
>
> Alcoholism should be subdued with fasting and emesis.
>
> In circumstances where there is excessive Kapha in the body; pain, heaviness and coldness can be observed, appropriateness of consuming pungent and hot products and there is a certain desire for workout and fasting.
>
> (Sharma, 2007)

According to Professor Dr Vasant Lad,

> Before observing a fast, the constitution of an individual's body must be considered. In western countries, people occasionally fast for several days ranging from 10–20 or more days without identifying the constitution of their body, and this insufficiency of understanding and knowledge regarding constitutions may have injurious effects.

For example, an individual with *vata* constitution should not continue fasting for more than three days, as fasting may enhance lightness in the body and *vata* (air of

body) is light too. Ultimately fasting may affect the *vata* element. If fast persists for a longer duration of time, it will enhance anxiety, weakness, fear and nervousness. Similarly, people with *pitta* constitution shouldn't fast for more than four days or else it will provoke *pitta*, enhancing the element of fire in the body, and it will be the reason for some reactions of mind and body such as hate, anger and dizziness. Whereas individuals with *kapha* body may observe fast for a longer duration, and they will get maximum benefits after fasting such as enhancement of clarity, consciousness, awareness and understanding; moreover an increased feeling of lightness.

If an individual is on juice fasting, it is noteworthy to keep in mind that apple juice is beneficial for the *kapha* body; pomegranate juice is for the constitution of *pitta*, whereas grape juice is for *vata* constitution. Ayurveda instructs that during fasting, particular spices and herbs such as cayenne pepper, black pepper and ginger that have medicinal properties due to their spicy and hot characteristics may be consumed to aid in toxin neutralisation in the system. If these herbs are consumed in the tea form, they will assist in igniting the *agni* (fire), which will then burn the toxic material away. Fasting is advised when there is constipation, fever, arthritis and cold. If toxic materials are present in the large intestine, fasting should be observed. Fasting is suggested at least once a week, and it permits the gastrointestinal tract to cease work in order to relax and regain strength.

Rigveda, which is one of the ancient Vedic Sanskrit texts, mentions that the desire for longevity and health is revealed in the Veda *sukt*, which means 'Allow me to observe 100 autumns, and allow me to survive for 100 autumns'. Ayurveda recommends the intake of fruits, whole grains, vegetables and foods, moreover avoiding food that has a minimum amount of *prana* (life energy) such as frozen, refined, overcooked, over-ripened and highly processed food products. Meanwhile, in accordance with the Hindu culture, a well-balanced lifestyle that encourages physical and mental health, supporting longevity, is advised (Tiwari & Pandey, 2013).

Fasting in Christianity

In Christianity, fasting is carried out during Good Friday in the memory of Jesus Christ. It is to refrain from meat throughout this day. It describes a single meal per day or two meals of smaller quantities which must not surpass the quantity of the main meal. It is also highlighted that people between the ages of 18 and 59 will be permitted to fast on this day. However, pregnant women, older people, sick individuals and patients with any psychiatric disease are free from the obligation of observing fast. A number of times fasting has been mentioned in the Holy Bible. A few examples are: Moshe Rabbenu (Moses) also observed fasting for 40 days and nights two times consecutively, devoid of water or food; initially, instantly prior to accepting the tablets from God on the mountain, while the second time, subsequent to his arrival downward, and observing the Israelites carrying out idolatry and shattering the tablets in annoyance (Craigie, 2007; Natarajan et al., 2014). Christians usually follow two types of fasting that are discussed in the following sections.

Greek Orthodox Fasting

Orthodox fasting (OF) is a seasonal kind of fasting observed during Lent (the period prior to Easter), Nativity (birthday of Jesus Christ) and the Assumption

(Trepanowski & Bloomer, 2010). Orthodox fasting comprises of regular refrainment from eggs, fish, dairy products, olive oil and meat on Wednesdays and Fridays. Throughout orthodox fasting, practitioners of the fast take vegetables, bread, seafood, nuts and fruits (Sarri et al., 2003). Orthodox fasting commonly consists of 180–200 days of fasting each year – 40 days before Christmas (Nativity fasting), 48 days before Easter and 15 days before the Assumption, in addition to single supplementary days of fasting such as Epiphany Eve. The consumption of alcohol is also prohibited during orthodox fasting (Trepanowski & Bloomer, 2010). There are minimal publications concerning the impact of orthodox fasting on the health of humans; however, it is worth mentioning that it is a persistent pattern of the diet with reliable constancy regarded as a Mediterranean diet, and performed long enough to justify exploratory research because of its actual possible physical effects (Venegas-Borsellino et al., 2018).

The consumption of both trans fat and saturated fats reduce during the fast, while the intake of monounsaturated fat does not modify (Papadaki et al., 2008; Sarri et al., 2009; Sarri et al., 2004). Moreover, the consumption of PUFA (polyunsaturated fatty acids) may or may not reduce throughout the period of Greek orthodox fasting with regards to the intake of minerals and vitamins; consumption of both calcium (Papadaki et al., 2008; Sarri et al., 2007, 2009; Sarri et al., 2004) and riboflavin diminish during fasting. On the contrary, the consumption of magnesium enhances throughout these durations (Papadaki et al., 2008; Sarri et al., 2007). Concerning the anthropometric consequences, body mass index may or may not lessen during fasting (Sarri et al., 2009; Sarri et al., 2003). Furthermore, the average body mass of Christian monks (Greek orthodox) was noticed to reduce during a week of fasting by a number that reached significance (Papadaki et al., 2008). With respect to biochemical findings, levels of both low-density lipoprotein and total cholesterol reduce during fasting (Papadaki et al., 2008; Sarri et al., 2009; Sarri et al., 2003). Another study stated a reduction in the levels of high-density lipoproteins (Sarri et al., 2003), while other research experiments mentioned no change (Papadaki et al., 2008; Sarri et al., 2009). There are inconsistent findings on the outcomes of blood pressure in Greek orthodox fasting; one of the studies established that levels of SBP enhanced during fasting durations (Papadaki et al., 2008), while another study identified no change in BP when non-fasting persons were contrasted with fasting persons (Sarri et al., 2007).

Biblical-Based Daniel Fast and Its Health Benefits

A well-known fast observed by Christians is the Daniel fast, which originated from the story of Daniel (1:8–14 NIV), in which Daniel decided not to spoil himself with wine and royal food and asked for permission from his leader to take nothing except water and vegetables for around ten days. Afterwards, in the same book, again Daniel pursued a 21-day fasting period; throughout this period, he neither consumed meat nor wine. Based on these two readings, currently, the Daniel fast includes the consumption of particular foods as much or as often as desired; however, the choices of food are bound to legumes, vegetables, oil, nuts, fruits, seeds and whole grains. This plan has qualities similar to the vegan diet, which has been stated to produce health-improving properties (American Bible Society & International Bible Society, 2011).

A Daniel fast may be perceived as a type of dietary restriction, though, unlike an uncomplicated vegetarian diet or Christian Greek orthodox fasts, a Daniel fast

is considerably most strict; this is due to white flour, sweeteners, alcohol, preservatives, caffeine, additives, refined foods and flavourings being prohibited (American Bible Society & International Bible Society, 2011). In spite of that, since people traditionally observe and act according to the Daniel fast for strict associations with their religion in an effort to get nearer to God throughout a duration of sustained prayer, exploratory scientific research and anecdotal records have demonstrated splendid compliance. The Daniel fast is generally manifested for 21 days, however, as short as ten days to as long as 40 days have been reported (Bloomer et al., 2010).

This has been shown in experiments conducted on animals in which alterations in diet (generally by means of controlling protein or methionine) has been related to longevity and amelioration of health (López-Torres & Barja, 2008). In human experiments, it has been observed that 'natural or organic' food items, for instance, seeds, vegetables, nuts, fruits and whole grains, which are devoid of or have a very small amount of preservatives, while limited or no amount of saturated lipids, together with ample micronutrients and fibre, may give health-promoting effects (Bloomer et al., 2010).

Remarkable compliance has been observed with the fast (>98%) and an outstanding outcome for overall satiety and moods. As anticipated, a decline was observed in the succeeding variables from seven days before beginning the fast to the ending seven days of the fast: protein, cholesterol, trans fat, total kcal, saturated fats and total fats. Moreover, a rise was observed in fibre, carbohydrate and vitamin C. The succeeding variables associated with risk of cardiovascular disorders were considerably decreased after the fast contrasted with before the fast: low-density lipoprotein, total cholesterol, systolic and diastolic blood pressure. C-reactive protein, insulin and homeostatic model assessment for insulin resistance were all decreased to a clinically significant range; however, this reduction failed to attain significance statistically.

Because of the strong reduction in total cholesterol, high-density lipoprotein cholesterol was decreased after the fast in contrast with before the fast. The aforementioned findings signify that a Daniel fast for 21 days can improve numerous indications of overall health conditions. Randomised studies of a wider scale are required to expand this introductory data. Research in future should hopefully contemplate increasing the period of the fast, as well as altering the choices of food in an attempt to improve or maintain the levels of high-density lipoprotein (Bloomer et al., 2010; Trepanowski & Bloomer, 2010).

Fasting in Buddhism

The fasting methods in Buddhism comprise a particular vegetarian diet, which is carried out all year round. The category of food differs among various cultures and countries, i.e. Buddhists from China particularly take milk, while on the contrary, Buddhists from Taiwan take soybean products (Chen et al., 2008; Lee & Krawinkel, 2009). Facts and figures considering these differences are not accessible. Intake of alcohol, pungent vegetables (such as onion, garlic, leeks) and processed foods are forbidden (Persynaki et al., 2017). Generally, vegetarian diets have been related to protection from cardiovascular ailments and longevity. Deficiencies of micronutrients are little because of milk intake. Research studies have revealed that even with lessened caloric and calcium (↓330 g/day) consumption regularly, diminished BMD

(bone mineral density) was not established (Ho-Pham et al., 2009). The particular vegetarian diet in Buddhism has contemplated a dietary restriction, which has been related to enhanced longevity. One of the studies revealed that those nuns who were vegan consumed decreased amount of calories and calcium devoid of any considerable effect on densitometry of bone minerals (Ho-Pham et al., 2009).

Danjiki, a traditional ascetic custom in the Buddhism practice of Japan, includes meditation, fasting and physical workout. It needs significant physical and mental regulations to combine spirit, body and mind to gain enlightenment. Recently, a range of Danjiki customs varies from short-period fasting, protocols that are carried out at a hotel with medical supervision, to extensive fasting terms, the protocols of exercise managed at a temple of Buddhists. There are plentiful anecdotal proofs that a range of advantages of the Danjiki custom includes detoxification, weight loss, happiness and sharpened senses. Though, the custom's diligence and arduous nature may nullify or even antagonise the possible fasting benefits. Despite the admiration of this lifestyle alteration, there are no data from studies regarding the outcome of the prolonged Danjiki fasting custom on cardio-metabolic health indicators and adiposity (Tanaka et al., 2016).

Potential Health Benefits of Intermittent Fasting

It is one of the diet patterns in which the feeding and fasting period cyclically takes place; intermittent fasting may consist of time-restricted or alternate-day fasting. Islamic fasting is similar to alternate-day fasting because the feeding and fasting periods in Islamic fasting vary between 12 to 18 hours typically on average based on geographical location and season of the year. Time-restricted fasting is a kind of intermittent fasting, in which the person consumes calories for the entire day within just about eight hours while fasting for the remaining hours (Pakkir Maideen et al., 2017).

Intermittent fasting, an antique compulsory practice carried out by Muslims throughout Ramadan (for more than 14 hours consecutively for 30 days from daybreak to dusk), gives rise to up-regulation of essential modulatory proteins of metabolism, immune system and repair of deoxyribonucleic acid in addition to it resulting in a protective effect against inflammatory disorders and inflammation-related lifestyle ailments. Intermittent fasting decreases inflammation and hence could provide a number of encouraging benefits to health in specific conditions of diseases, for instance, rheumatoid arthritis, asthma and obesity, to which inflammatory reaction is essentially involved. Fasting increased insulin sensitivity and encouraged stress resistance in cells, and therefore assisted in developing flexibility in immune reaction. Intermittent fasting made the clinical outcomes better and originated a decrease in the inflammatory biomarkers such as serum tumour necrosis factor-α and oxidative stress in patients with asthma. The prospective fasting molecular mechanism includes stimulation of adaptive stress responses in cells that leads the host's defence system to antagonise the severe forthcoming stress and respond to pathogenesis.

A drop in fat mass is associated with a drop in proinflammatory cytokines in the blood, which suggests that methods developed to promote fat loss could particularly have favourable outcomes and subdue the proinflammatory disorders related to obesity. Intermittent fasting could assist in regularising the body's systemic

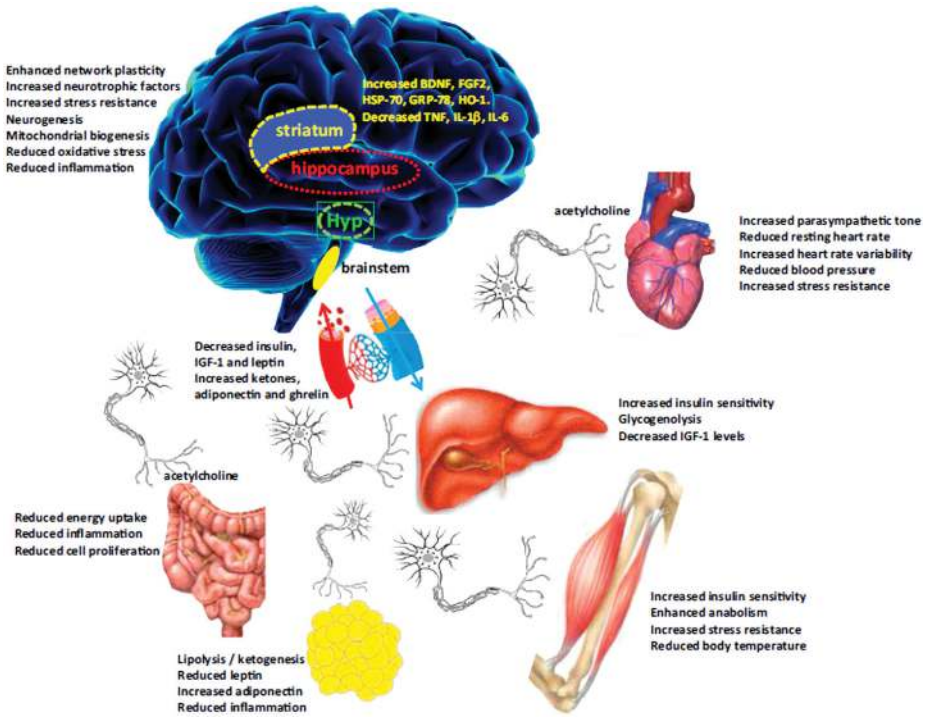

Figure 3.1 Potential effects of intermittent fasting on major organ systems. (Source: illustration acquired from *Fasting: Molecular Mechanisms and Clinical Applications* [2014] Valter D. Longo, and Mark P. Mattson, Cell Metabolism.)

inflammation status by subduing TNF-α, IL-6 and IL-1B while reducing the levels of circulating leukocytes and fat mass. By encouraging these findings, another study demonstrated that intermittent calorie restriction constructively regulates the pathways of proinflammatory cytokines by inhibiting the levels of adipokine and serum cytokines in C57BL6 (wild kind of female rodent) (Hannan et al., 2020) (Figure 3.1).

SARS-CoV-2 and Fasting

The rising morbidity and death rate from many pulmonary disorders, including coronavirus disease 2019 (COVID-19), are ascribed to enhanced unnecessary production of cytokines, uncontrolled infiltrates of inflammation and antibody-reliant intensification that ultimately leads to pulmonary tissue destruction (Li et al., 2020). The storm of cytokines in patients with COVID-19 is distinguished by enhanced interleukin-6, IL-1b, IL-37, IL-17, IL-38, interferon-α and interferon-β (Li et al., 2020). On the contrary, intermittent diurnal fasting during Ramadan has a constructive effect on the complete status of inflammation in the human body and inclines to reduce such cytokines responsible for causing inflammation, especially IL-6, IL-1b and chemokines CXCL10, CXCL 1 and CXCL 12, which might reduce the pulmonary tissue destruction. The intermittent fasting of Ramadan has

a harmonising outcome on macrophages and leads them to synthesise decreased quantities of cytokines, formerly established to positively influence the subjects of asthma (Abunada et al., 2020).

The possible immune-dodging process of severe acute respiratory syndrome coronavirus 2, which includes viral protein ORF3a-arbitrated continuous stimulation of NLRP3 (NLR family pyrin domain containing 3), can also be regulated by intermittent fasting. Throughout intermittent fasting, conventional metabolism of energy shifts ideally towards the catabolism of fat and the synthesis of ketone bodies as immediate energy sources. The BHB (β-hydroxybutyrate), a significant ketone body that nourishes many vital organs throughout starvation and/or fasting, may also aid in alleviating inflammation by obstructing the over-stimulation of NLRP3. As obvious in investigational models, β-hydroxybutyrate decreased the synthesis of interleukin-1 beta and interleukin-18 arbitrated by inflammasome NLRP3 in monocytes of humans and repressed stimulation of interleukin-1β and caspase-1 synthesis in rodents (Hannan et al., 2020).

Effects of Fasting on Various Hormones

Intermittent fasting and calorie restriction may escalate adiponectin levels in both animals and humans (Mazaki-Tovi et al., 2005; Wan et al., 2010). Adiponectin (the distinct adipocyte protein) is inversely associated with insulin resistance, body weight and adiposity (Okamoto et al., 2008). Adiponectin decreases the dysfunction of pancreatic β cells and inhibits insulin levels, moreover harmonising the activity of insulin (Cui et al., 2011; Retnakaran et al., 2005). Usually, patients with diabetes have decreased adiponectin levels (Bik et al., 2006). In contrast, enduring and healthy individuals have escalated levels of adiponectin, such as the dwarf Ames mouse which has three times more adiponectin than the control mouse (Golbidi et al., 2017). It is contemplated that the tendency of adiponectin to modify metabolism from burning glucose to burning fat decreases oxidative stress while alteration in the diet of four rodent strains strongly proposes that the quantity of calories is the principal determinant for secretion of adiponectin instead of fat content. Adiponectin also moderates the benefits of intermittent fasting on the cardiovascular system as demonstrated in animal models (Golbidi et al., 2017); though its prognostic usefulness in human ailments has been suspected as increased levels of adiponectin are related to unfavourable consequences in CHF (congestive heart failure) (Mazaki-Tovi et al., 2005).

Metabolic Effects of Fasting

In a state of fasting, the hepatic glycogen is diminished in the initial 18 to 24 hours (Cahill, 1976), while the protein, which has indispensable mechanical, structural and enzymatic functions, makes up 15% of the overall total energy stores of the body. Due to these extremely important functions, the disintegration of a third to a half of the protein stock of the body is thought to be irreconcilable with life. Another place for stocking glycogen is muscles, which start lacking glucose-6-phosphatase and hence can't directly liberate glucose into the blood circulation (Saudek & Felig, 1976). Lipid in the state of triglyceride in fatty tissues gives the body the greatest

and most productive energy storage and accounts for 85% of all possibly accessible calories. On average, a 70-kilogram individual requirement of basal calories could be fulfilled merely from lipid stores for around two to three months in the lack of any caloric consumption (Kerndt et al., 1982; Saudek & Felig, 1976).

Fasting and Diabetes Mellitus

A well-known modus operandi of intermittent fasting includes a whole day of consuming food and drink followed by a fasting day; however, others proposed 20 hours of fasting followed by four hours of eating period or 16 hours of fasting then eating for eight hours (Barnosky et al., 2014). Numerous research trials have contrasted calorie restriction with intermittent fasting, though up till now there is no study comparing the different protocols of intermittent fasting with each other. One study compared calorie restriction and intermittent fasting in patients with type 2 diabetes mellitus (Varady, 2011); they established that although calorie restriction is better with reference to reduction in body weight, intermittent fasting and calorie restriction (CR) had similar effects in reduction of visceral fat, insulin resistance and fasting insulin. In nondiabetic persons, intermittent fasting enhances metabolic parameters (Anson et al., 2003).

Intermittent fasting (IF) decreased fat mass while maintaining the body's lean mass, contrasting with regular calorie restriction, which results in decreased lean and fat body mass (Colman et al., 2009; Ding et al., 2016). Modifications in a diet are a crucial factor in the treatment of diabetes. In one of the longitudinal (20 years) studies of rhesus monkeys, calorie restriction decreased age-associated disorders including diabetes, in which five out of 38 animals from the control group experienced diabetes while another other 11 became prediabetic, whereas the animal undergoing calorie restriction demonstrated no abnormality in the homeostasis of glucose (Hamman et al., 2006). Intermittent fasting may cause identical results in both prediabetic and diabetic persons, as only a 1 kilogram decrease in body weight is related to almost 16% inhibition in risk of diabetes (Clément et al., 2004). Several studies endorse the efficiency of intermittent fasting in minimising risks and complications of diabetes, i.e. IF decreases fat of viscera, a significant site for giving rise to tumour necrosis factor-α in patients of diabetes (Eshghinia & Mohammadzadeh, 2013). Inhibition of visceral fat following around 42 to 168 days of intermittent fasting has been documented in numerous research studies (Golbidi et al., 2017).

Fasting and Its Effects on Obesity and Metabolic Syndrome

Metabolic syndrome is characterised by central obesity in combination with increased triglycerides, insulin resistance and/or high blood pressure and significantly enhances the risk of stroke, diabetes, cardiovascular disorders and Alzheimer's disease. Rodents kept under the regular ad libitum feasting situation cultivate a metabolic syndrome–like phenotype while they age. Metabolic syndrome can also be caused in young animals by giving them a diet rich in sugar and fat (Martin et al., 2010). Intermittent fasting can reverse the condition and prevent rodents from all features of the metabolic syndrome, i.e. blood pressure, abdominal adiposity and inflammation are inhibited, sensitivity of insulin is escalated and

the functional abilities of neuromuscular, nervous and cardiovascular systems are ameliorated (Castello et al., 2010; Wan et al., 2003). A preventive effect of fasting against renal and hepatic damage occurs instantly, with 24–72 hours of fasting making the functional consequences better and inhibiting tissue damage and death rate (Mitchell et al., 2010). Various hormonal modifications that symbolise metabolic syndrome in humans are noticed in rodents kept on high sugar and fat diets, counting increased levels of leptin and insulin but decreasing levels of ghrelin and adiponectin. Rising levels of leptin are particularly reflective of a proinflammatory condition, while on the contrary, ghrelin and adiponectin can subdue inflammation and enhance the sensitivity of insulin (Baatar et al., 2011; Yamauchi et al., 2001).

Effects of Fasting on Cancer

Fasting can have constructive outcomes in the prevention and management of cancer. In rodents, alternate-day fasting (ADF) brought about a significant reduction in the occurrence of lymphomas (Descamps et al., 2005), and one day of fasting per week impeded the spontaneous development of tumours in P53-lacking rodents (Berrigan et al., 2002). In animal models of metastatic tumours, amalgamations of cancer treatments and fasting that cause differential stress sensitisation and differential stress resistance result in 20 to 60% carcinoma-free endurance contrasted with fasting or chemotherapy alone, which are usually not enough to give rise to any carcinoma-free survival (Lee et al., 2012; Shi et al., 2012).

Effects of Fasting on the Immune System

Long-term or periodic fasting has a more noticeable influence on immune reactions and metabolism than short-period fasting or calorie restriction; for instance, alternate-day fasting and time-restricted fasting (Cheng et al., 2014). Further research studies have also shown that fasting during Ramadan persuades the expression of anti-inflammatory and antioxidant genes in both healthy participants and non-diabetic obese individuals (Faris et al., 2019; Madkour et al., 2019). Fasting also decreases the levels of insulin growth factor-1, glucose, amino acids and insulin, with the stimulation of adenosine monophosphate-activated protein kinase and repression of mTOR (mechanistic target of rapamycin) signalling. In reaction to these metabolic changes, durable hematopoietic stem cells endure regeneration, stress resistance and self-renewal (Cheng et al., 2014). Time-restricted feeding may also bring about its effects autonomous of the decrease in consumption of total calories since time-restricted feeding was revealed to subdue weight gain and improve inflammation, hepatic steatosis and hyperinsulinemia in rodents feasted on a high-cholesterol diet (Hatori et al., 2012).

Fast mimicking diets or periodic fasting and re-feeding have been demonstrated to encourage immune cells regeneration and trigger haematopoietic stem cells (Cheng et al., 2014), regulate microbiota of the gastrointestinal tract, mitigate pathologic conditions in different autoimmunity models of rodents (Choi et al., 2016; Cignarella et al., 2018; Rangan et al., 2019) and encourage the T cell–reliant destruction of cancer cells (Di Biase et al., 2016; Pietrocola et al., 2016). However, the mechanisms accountable for these outcomes of periodic fasting on immunity remain

inadequately known. Collins et al. revealed increased prevention against tumours and infections when merely a 50% restriction of the calorie pertained in place of only water fasting (Collins et al., 2019). This research enhances the probability that absolute nutrient deficiency, but not the incomplete conditions of fasting, may result in several impairments in the immune system (Buono & Longo, 2019).

One of the research experiments analysed the outcome of Ramadan fasting on the body's capacity to combat pathogenic microbial contamination of *Mycobacterium TB* (causative agent of tuberculosis) in around 30 fasting participants (Lahdimawan et al., 2014). It showed that fasting in the month of Ramadan was linked with a decrease in the microbe's pathogenicity by enhancing the number of macrophages. The research also demonstrated the propensity of fasting to enhance interferon-gamma secretion, which is recognised to promote the anti-bacterial immune mechanisms in opposition to numerous viral and bacterial infections (Lahdimawan et al., 2014).

Contemporary research studies demonstrated that time-bounded re-feeding and periodic fasting would strengthen the immune system. Of record is that Müller et al. revealed that the therapeutic utilisation of periodic fasting decreases rheumatoid arthritis symptoms when followed by a vegetarian diet (Longo & Panda, 2016). Comprehending the mechanistic association between the benefits of fasting and nutrients leads to recognising FMD (fasting-mimicking diets) that acquire alterations identical to those brought about by fasting (Longo & Panda, 2016). Cheng et al. showed the impact of periodic fasting in encouraging a haematopoietic stem cell–reliant regeneration of rodent's immune cells, heading to a re-invigorated phenotype of the immune system and escalation of MSPC (mesenchymal stem and progenitor cells) even in a comparatively old-age rodent (Cheng et al., 2014; Longo & Panda, 2016). Re-feeding and fasting cycles have been demonstrated to regulate the microbiota of the gastrointestinal tract, mitigate pathological conditions in several autoimmunity models of rodents and stimulate T cell–reliant destruction of cancer cells (Buono & Longo, 2019). Dang et al. demonstrated that fasting increases TNF-related apoptosis-inducing ligand-mediated hepatic NK cell activity in opposition to neoplastic cells by means of HSP70 up-regulation (Dang et al., 2014). In accordance with the anti-inflammatory effect of fasting-mimicking diets in rodents, Brandhorst et al. showed that mesenchymal stem and progenitor cell levels were elevated shortly during fasting-mimicking diets in human subjects (Brandhorst et al., 2015; Longo & Panda, 2016).

Fasting Enhances the Expectancy of Life

The ageing process is related to the progressive loss of the function of different organs and enhanced susceptibility to disorders. Authentications propose that intermittent fasting considerably brings about the augmentation of lifespan (Longo & Mattson, 2014; Mercken et al., 2012) by endeavouring anti-ageing effects; for instance, the decrease in cardiovascular ailments, cancer, metabolic-diabetic indicators, oxidative injury and by raising stress resistance in cells (Mattson & Wan, 2005; Sohal & Weindruch, 1996). At the same time, CR may increase the levels of the hormones subduing inflammation (e.g. ghrelin and adiponectin) and diminish the hormone levels controlling metabolism, thermogenesis and anabolism in cells (such as Leptin, estradiol, testosterone and insulin) to demonstrate anti-ageing outcomes (Fontana & Klein, 2007).

Alternate-day fasting has been related to a drop in BP and a rise in the sensitivity of insulin, as well as slowing down the outset of metabolic disorders (Mattson & Wan, 2005; Varady & Hellerstein, 2007). Calorie restriction is related to improving mental sharpness and intelligence; however, the purpose of religious fasting is cleansing the body and soul, intending to acquire spirituality. The extended durations of fast possibly have a more considerable impact on body weight, parameters of oxidative stress, cardio-metabolic risk indicators and overall health (Persynaki et al., 2017).

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Chapter 4

Cupping Therapy and Immune System

Introduction

Cupping therapy is among the most ancient and extremely effective methods for the elimination of toxins. It cleanses a particular part of the body more effectively than venesection (a form of bloodletting that removes blood from the blood vessels) does. Cupping was, and still is, performed widely in its different types among a lot of regions around the world, including the UK, USA, South Asia, Middle East, Africa, Europe, etc. because it is a part of several primaeval systems of healing, for instance, Chinese, Ayurveda, Greco-Arabic, Tibetan, Korean and Oriental medicine (Qureshi et al., 2017). It is considered a low-cost and easily accessible way of preserving good wellbeing, preventing ailments and managing an extensive range of diseases. This antique therapy has profound ancient roots in Chinese culture and has been an essential part of TCM for thousands of years. The most primitive pieces of evidence of cupping therapy in China are established in a manuscript written on silk, or 'Bo Shu', discovered in a historical mausoleum of the Han Dynasty. A well-known proverb in China notifies us that: 'Cupping and Acupuncture, over half of the disease treated' (Chirali, 2007). Moreover, Eber's papyrus (one of the most ancient medical manuscripts of the globe since 1550 BC) also talks about cupping therapy. In Ayurvedic medicine, cupping is a part of 'raktamokshana panchakarma' along with venesection and leech therapy to keep the *doshas*, *rakta* (blood) and *rasa* (body fluids) in the appropriate balance (Suśruta & Srikanthamurthy, 2010). It can be applied either as individual therapy for chronic and reappearing diseases, for instance, rheumatoid arthritis, or jointly with complementary methods such as acupuncture or massage, or in amalgamation with conventional medicine as associates of integrative medicine. The cupping therapy is practised by applying cups to specially chosen points of skin and generating a negative atmospheric pressure, either by suction or by fire. This procedure stimulates detoxification of body tissues, increases microcirculation, and alleviates excruciating tension in muscles. Subsequently, it may create a round patch distinguished by erythema, bruising and petechiae; however, these are not classically brutal and commonly fade away after

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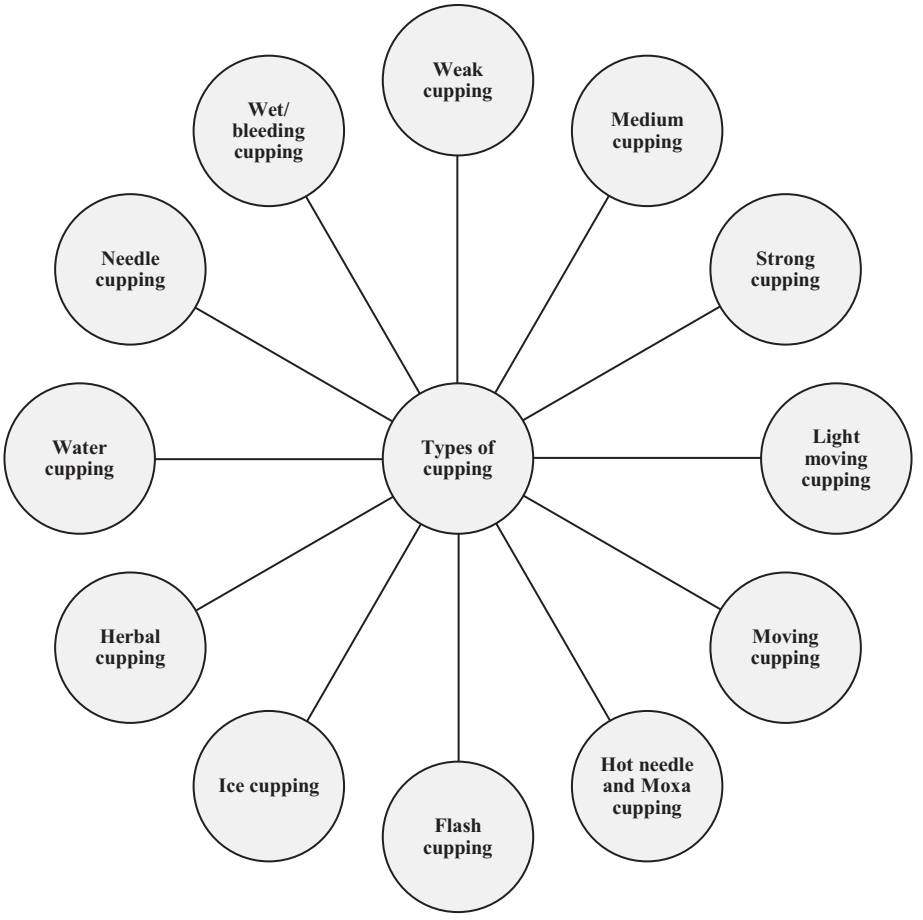

Figure 4.1 Methods of cupping. (Chirali et al. 2014)

one to two weeks. Despite that, many patients are still frightened of being treated with cupping and show distress about the noticeably displeasing spots that it leaves locally. People's faiths and beliefs can significantly manipulate the healing benefits and unfavourable effects of therapy. Optimistic expectations of the healing can increase its therapeutic efficiency, whereas pessimistic beliefs can weaken it (Hong et al., 2020). There are several ways to perform cupping depending on the patient's present condition. Chirali et al. discusses the 12 methods of cupping in their book (Figure 4.1). In contrast to venesection, cupping or wet cupping hardly ever causes a deficiency of red blood cells because a large number of red blood cells can't pass through the pores of capillaries simultaneously. Besides, it shifts and clears fluids of interstitium from surplus fluids and/or soluble contributing pathological matters that were stated to be rich in iron (Bashiri et al., 2020).

History of Cupping

In the past, before any archaeological or historical facts had been discovered to assist the use of cupping over the human body as a curative process, primaeval

humans depended partially on their capability to suck and pull any irritations towards the external surface of the body. A prehistoric man also discovered the process and formed a concept regarding their position in the universe and nature, moreover the reasons for weaknesses and diseases. People recognised from existing artefacts that cupping was generally practised by the time of primaeval Babylonians, the Egyptians in the era of the earliest Egyptian rulers, and the most primitive Chinese. At these times cupping was executed sometimes by using shells, horns, stones, metal cups, parts of bamboo trees or bull's horns, with the help of which air was eradicated by strong sucking (Skinner, 1996). In their attempts to elucidate disease, they held convictions about that which could penetrate the mind or body, for instance, wicked spirits could be the reason for afflictions and pain. Lots of investigators, including anthropologists, have illustrated how therapists of these supernaturalistic practices of disease causation put suction by their mouth to the surface of the patient's body to remove the effects of these malicious powers (Jackson, 2001; Sagi et al., 1988; Xie et al., 1996). Though there is a rationale to consider that the practice dates from as early as 3000 BC, the most primitive evidence of cupping is in the Ebers Papyrus, which explains Egyptians made use of cupping. Archaeologists have established proof of cupping in China earlier in 1000 BC. In the era of the Greeks, Hippocrates applied cupping for the ailment of internal organs and structural complications. Cupping in the Middle East was encouraged by some very well-known physicians like Ibn Sina (AD 980–1037), Abu Bakr Al-Razi and Al-Zahrawi (Aboushanab & AlSanad, 2018). In the Middle East and the European regions, cupping was expanded from humoral medicine, the structure of health very old Greeks utilised to re-establish balance utilising the four 'humors' in the body: blood, phlegm, yellow bile and black bile (Sweet, 1999). Part of the force behind Galen's point of view in favour of local bloodletting or bleeding cupping came from his application of the humoral theory. This humoral theory has its basis in the idea of the four elements suggested by Pythagoras: fire, air, earth and water. Hippocrates and Empedocles would be from those who would later construct this theory to consist of four humours: blood, yellow bile, phlegm and black bile. Better health came consequently if the humours were in fine equilibrium, with a surplus, or 'plethora' of a humour exhibiting itself as fever or inflammation. For instance, colds and flu in winter were considered to be because of phlegm, diarrhoea in summer because of the bile and mania because of bile simmering into the brain (Mettler, 1947). In the earliest Babylonian empires, a massage technique was also applied to enhance the healing attained by cupping. In spite of lots of criticisms, the procedure of bloodletting had turned out to be a standard clinical practice by the time of Galen (130–200 AD) (Hamilton, 2002).

Cupping in European Regions

Among the most primitive published medical manuscripts, the 'Calendar for Bloodletting' was the one dispensed in 1457. These calendars, recognised as Aderlasskalender, turned out to be very trendy in some European regions, comprising celestial symbols and a figure of a man. Thomas Mapleson, the author of 'A Treatise on the Art of Cupping' advised cupping as a superior form of bleeding for the subsequent list of ailments in which cupping can be applied with advantage: bruises, haemoptysis, peripneumony, asthma, bleeding within internal organs and accompanying symptoms, catarrh, erysipelas, lethargy, pleurisy, chest pain, cough, giddiness, cramps, contusion, convulsion, delirium, hip and knee disorders, gout,

inability to hear sounds, dropsy, epilepsy, eruptions, pertussis, hydrocephalus, headache, pneumonitis, intoxication, insanity, lumbago, measles, limb numbness, obstructions, inflammation of the eye, paralysis, defective perspiration, rheumatism, sciatica, SOB, sore throat, pains of the side and chest and to obtain rest (Mapleson, 1830). Just about at the same time, Benjamin Rush, one of the signatories of the Declaration of Independence in America, supported extensive bleeding for the period of the yellow fever outbreaks. In 1793 he told a mass of people, 'I manage my patients efficiently by bloodletting and abundant eradication with Mercury (I) chloride [white powder used as purgative] and jalap [a purgative or cathartic drug used for purgation]', and he also advised the people to employ the same methods of healing. He said to 'lose blood and purge all Kensington' (King, 1971). A number of the most vivid pictures showing the past of bloodletting originated from the period of the barber doctors of Europe (western regions). Lanfranc, an exceptional French surgeon in 1315, expressed dissatisfaction about the propensity of surgeons to leave the bloodletting to women and barbers, though this practice would be carried on during the 17th century (Flynn, 1994). King Henry VIII (of England), signed a declaration to combine the two groups into the vast corporation of Surgeons and Barbers. The shops of barbers turned into a location where clients could obtain a bloodletting, dental removal and a haircut, everything at a single place and in a single visit. This method of cupping has been utilised by doctors of allopathic medicine for numerous centuries to manage a variety of diseases, concluding in peak practice in the mid-18th century. Afterwards, there was a quick refusal of cupping, for many causes (Hamilton, 2002), including that the practice was forcefully opposed by the recently produced qualified associations of doctors who considered it an outdated practice. Despite the disgracing and dishonouring of humoral theories and their substitution by contemporary elucidation of diseases coupled with the uprising of chemical-based drugs preferred for the same ailments usually targeted by cupping, there has been a visible restoration of interest and surge of popularity for the procedure in recent times and the application of cupping is also rising strikingly (Avicenna et al., 2014; Bhikha & Saville, 2015) (Figure 4.2).

Hippocratic Views about Cupping

Written and documented verification of cupping can be established in the inscriptions of Hippocrates (recognised as the father of contemporary medicine). Throughout the golden period of the initial state of Greek, Hippocrates and his admirers were committed to a practical approach to cure diseases and attempted to find realistic justifications for why people got unwell. They entirely rejected sources like ghosts or spirits and in their place explained that a deprived or unbalanced diet, inadequate workout, contact with unfavourable weather conditions, emotional aspects and a disturbed lifestyle were the principal agents of sickness. In his guide to clinical management, Hippocrates advised cupping for the management of menstrual diseases, angina and other ailments (Vaskilampi & Hänninen, 1982). He explained the practical phases of both dry and blood cupping. He seemingly favoured dry cupping, as this was less invasive and disturbing than wet cupping, milder and better suited to his well-known theory: 'First do no harm'. A significant focus of cleanliness practice in Greco-Arabic medicine is stimulating the eradication of toxins and wastes from the body. The cause is that their build-up leads inevitably to enhanced illness and

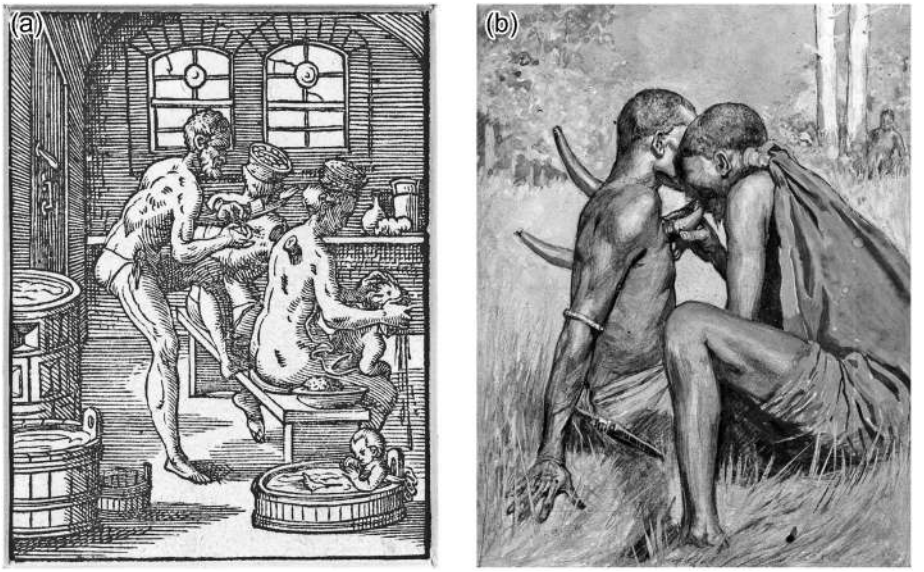

Figure 4.2 Medieval view of cupping therapy. (Open source courtesy: Wellcome Institute Library, London.)

possibly fatality. In diseases, for instance, urinary retention, constipation and some menstrual abnormalities, cupping is believed to advance eradication by enhancing the lymphatic flow and bloodstream in the body. The School of Hippocrates also believed that all ailments were the consequence of a disproportion in the body of the four humours: blood, yellow bile, phlegm and black bile. When these fluids are in perfect ratio, the individual gets pleasure from good health. But if the balance of humours is critically altered, he or she will die from the results of that particular illness. All the treatment modalities suggested by Hippocrates, including cupping therapy, were thus intended for restoring synchronisation between all four humours of the body. Additionally, lots of statements made about cupping are considered as being entirely unreliable because they were based on personal views and observations and not supported by strong scientific verification. Currently, though, numerous studies have been presented illuminating the importance of cupping, either unaccompanied or complemented by other treatment modalities, in a variety of general diseases (Bhikha & Saville, 2015) (Figure 4.3).

Wet Cupping Therapy or Hijama

The wet/bleeding cupping method is recognised in the Arabic world as hijama—the word hijama means 'to bring back to fundamental size' or 'to reduce in volume'. The application of hijama/bleeding cupping has been well-known in the Islamic world for hundreds of years. It has been considered a fundamental aspect of surgery. It was frequently performed in the majority of hammams or Turkish baths together with other complementary and alternative therapies such as massage therapy, hirudotherapy, venesection, hydrotherapy, etc. The Prophet Muhammad (PBUH)

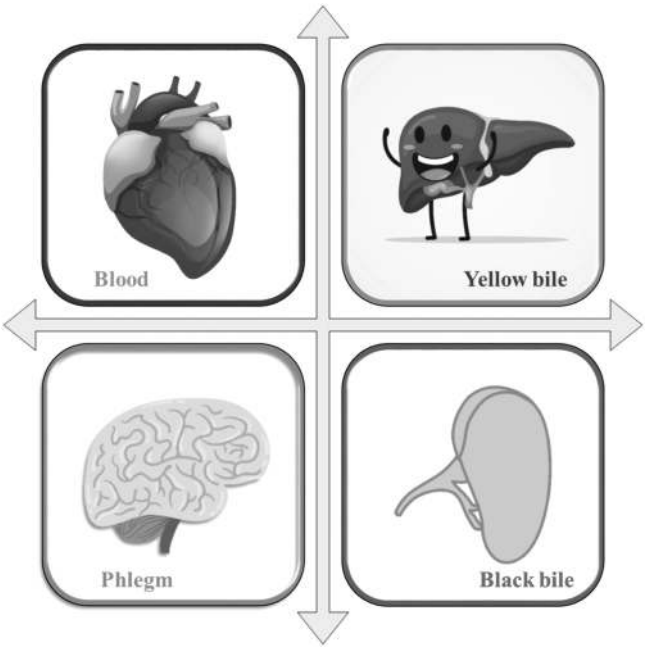

Figure 4.3 Four humours according to Hippocrates', Galen's and Avicenna's points of view.

is identified to have been a keen consumer and supporter of hijama cupping. In the book of Imam Ibn Qayyim Al-Jauziyah (1292–1350), *Healing with the Medicine of the Prophet*, cupping therapy is recommended for numerous diseases (Al Jauziyyah, 2003). Generally, it was not merely cupping that was recommended, but also the advantages of such a healing method and the sites of cups to be applied, depending on the disease and state of the patient, in addition to the accurate timing of such healing following the lunar calendar. Avicenna, the writer of *Al-Qanun Fi'l-Tibb*, said cupping is not favoured at the start of the month, for the reason that the different conditions of the body are not disturbed at the beginning of the month, nor is it favoured in the last part of the month, as by then it would have diminished. Cupping therapy is favoured in the middle of the month when the matters of the body gathered and turned out to be agitated (Avicenna et al., 2014). In diverse Hadith, Imam Ibn Qayyim Al-Jauziyah affirmed: 'the prophet of Allah (PBUH) used to have cupping therapy at the superior part of the back and jugular veins on the seventeenth, nineteenth or twenty-first days of the month'. The most favourable time for having the therapy done is two to three hours subsequent to taking a shower. Advice was also given relating to diet, fasting a day prior to the cupping, having abundant green leafy and other vegetables, keeping away from milk and its products throughout the duration and days of cupping. According to a Hadith: 'there is healing provided in 3 matters—a sip of honey, scratching with a blade for cupping and cauterising by fire. I prohibit my ummah (Muslim community) from cauterising by fire'. Similar to the skin, blood has a special role to play in traditional Chinese medicine from that of allopathic medicine. One of the most significant features of blood in traditional

Chinese medicine is that it holds life force (*qi*) which is the vehicular engine of blood. 'Blood and Qi are undividable by themselves. Qi introduces life into Blood; in the absence of Qi, Blood would be a motionless liquid' (Maciocia, 1989). Hijama wet cupping therapy fulfils three significant purposes: it maintains health, prevent ailments and manage a diverse range of diseases. Wet cupping is a part of complementary therapy and is now used by a great number of people, including doctors of conventional medicine, as it was recommended by lots of Chinese, Arabic and religious physicians in numerous countries. Wet cupping or hijama followed by dry cupping is the technique of applying small, shallow, superficial incisions over the surface of the body under the cup to protract the toxic and stagnant blood in that area which is obstructing the rest of the blood supply, functions of organs and other systems of the body. Bleeding cupping was the most supported and applied cupping technique amongst all, particularly by the early practitioners in Europe, as they used the technique of wet cupping in order to eliminate obnoxious blood, which was believed as the basis of illness, from the human body. It can be utilised in the management of an unexpected rise in BP and in the expulsion of pus from furuncles and boils, which signify a surplus of heated blood and immobilisation. Cupping controls the flow of blood and *qi*. It aids to protract and eradicate pathogenic causes, for instance, moisture and stagnant heat. Cupping also shifts blood and *qi* and unlocks the minute openings of the skin, thus provoking the elimination of pathogens by means of the skin itself (Chirali, 2007). Though cupping was not incredibly famous for the duration of the medieval period, it dates back as far as Hippocrates, who suggested cupping the breasts sequentially to alleviate immoderate menstruation (Davis & Appel, 1979) (Figure 4.4).

Method of Wet Cupping Therapy

The WCT is quite famous in traditional Greco-Arabic and Chinese medicine. It is considered more favourable than dry cupping because it eliminates the stagnant, toxic blood from the body by means of scarification, while dry cupping brings the toxins to the surface of the body, shifts them and makes the pathways and channels of the body free. Subsequently, the blood which is averted is then substituted by healthy blood. It is prudent to understand that the negative pressure by means of suction and making incisions are the two major methods of WCT. Consequently, the specific modifications at cellular or organ levels of the body can be seen after each method of cupping. Precise interventions could increase or repress the hormones of the body, or they might encourage or regulate immunity, or they may throw out injurious materials from the body, and ultimately this might alleviate the pain (Al-Bedah et al., 2019). The whole process of cupping is uncomplicated; it is the method in which rapid, dynamic pulsating strokes are applied meticulously to begin excitation in muscles; it is useful in the management of all kinds of pains related to a range of ailments. Moreover, it has the potential to improve the QOL (AlBedah et al., 2011). Each sitting of hijama wet cupping therapy requires around 20–60 minutes and could be executed in a few fundamental steps.

(1) The initial step is primary suction, in which the practitioner allots particular points for cupping and sterilises the whole spot. The cup with an appropriate volume is positioned in the chosen place, and the practitioner draws

Figure 4.4 Wet cupping therapy in a private naturopathy clinic in Karachi, Pakistan.

the air present in the cup by means of fire, manual or electrical suction. Subsequently, the cup is placed on the epidermis and left for a duration of three to five minutes.

(2) Following primary suction, incisions are made on the surface of the skin by means of scalpels/surgical blade number 15–21 (depending upon practitioner's practice), lancets, plum blossom needles or auto lancing devices which are also used in some cases, especially when there is a chance of delayed healing of incisions (as in diabetic patients) (Qasim Ali Al-Rubaye, 2012).

(3) After making incisions, cups are placed again at the same spot similarly for about three to five minutes, and the practitioner sucks the air inside the cup so that the blood can come out of the skin.

(4) Following the duration of three to five minutes, when blood starts to congeal, remove the cups carefully so that the blood can't spill from the edges of the cup, clean and disinfect the area. Now it depends upon the physicians whether they want to cover the area with adhesive bandages or leave the area open (Figure 4.5).

The most important variation between wet cupping and venesection is the blood's biochemical composition. A contrasting study of blood that is acquired from wet cupping confirmed that the quantities of triglyceride, LDL, Hb, RBC count, haematocrit and viscosity of blood were elevated in the blood of wet cupping (Hekmatpou et al., 2013).

Figure 4.5 Process of hijama wet cupping therapy.

Types of Equipment and Applications of Cupping

Significant information concerning the past of bloodletting (BL) has appeared from the tools utilised to carry out the course of action. Spikes, teeth of fish, thorns and sharpened stones were among the first tools utilised for cupping. Ultimately, two groups of equipment appeared: those utilised for common BL and those applied for local BL. For the procedure of common bloodletting, fleams, lancets and phlebotomes were quite famous. In the 15th century, the thumb lancet was established, and surgeons were shortly recommended to keep various sizes with them to be ready and equipped for different instances. For local or confined bloodletting, hirudotherapy and cupping have been the most extensively applied practices. The process of dry cupping includes applying suction to locomote blood away from the site of inflammation without making any scratch or incision. On the other hand, in wet cupping, suction is pursued by making small incisions in the skin that result in bleeding (Davis & Appel, 1979). The scarificator, an effortless octagon or square with numerous blades, was established somewhere close to 1715 and was shortly modified for bleeding cupping. The blades of the scarificator could be utilised up to 20 instances, being lubricated and dirt removed and wiped subsequent to each method by springing it into a part of sheep's fat (Figure 4.6).

Since the fame of bleeding cupping diminished in the mid-19th century, awareness and curiosity were gone in scarification, and the attempt revolved to producing a more efficient sealed syringe to generate suction for DC. Up till then, suction had been attained by introducing ignite into a cylinder for only some seconds before positioning it on the skin of the patient. It is fascinating to observe that as the fame of dry cupping started to descend in the initial part of the 20th century, doctors had handed on the duty of executing the practice to barbers, who would make window symbols marketing 'Cups for Colds' (Fido & Fido, 1996). Spring lancet was established in 1719, a tool that would turn out to be very trendy with German, American and Dutch doctors. Nowadays, suction can be employed by means of silicon cups or with electric or hand pumps, while bamboo, plastic, earthenware or glass cups are commonly used globally. However, surgical blades of various sizes are used for making the incisions in the case of wet cupping therapy (Lowe, 2017).

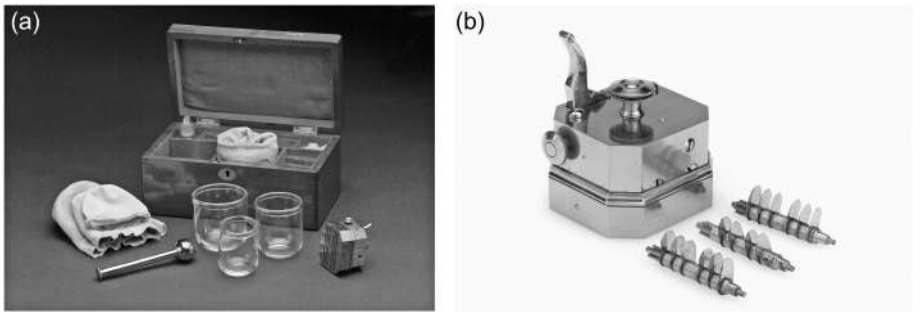

Figure 4.6 Cupping set along with brass scarificator. (Source: Wellcome Institute Library London.)

Physiological Effects of Cupping

Cupping is the practice of creating a fractional vacuum through suction or heat in one or numerous bell-formed containers to precise and distinct fractions of the skin. As soon as the cup is put in, centrally restricted negative pressure creates squeezing of the skin at the edge of the cup and interruption of the skin and core tissue inside the centre of the cup. The deepness of skin interruption, underlying muscle and fat is reliant on the sum of negative force applied and the diameter of the cup that is employed (Tham et al., 2006). The decreased pressure inside the device originates a pressure differential amid the surface of the skin and fundamental blood vessels, evoking almost instantly observable vasodilation of the capillaries existing on the surface, creating a localised uncontrolled upsurge of blood within the vascular system. There was five-times amplification in vascular perfusion within the area of vacuum reported in one research. Cups with a spacious diameter or better suction were related to enhancing perfusion (Cunningham et al., 2002). Enhanced blood flow in the muscles of the patients is maybe one of the natural processes that signify cupping has an effect on localised symptoms of pain (Liu et al., 2013). Eventually, the raised pressure in the vessels can be the reason for the bursting of capillaries with consequent purpura, petechiae or ecchymosis growing within the region of the cup (Cutter & Marquardt, 1930). The outcome of the extended suction is extravascular blood inside the subcutaneous tissue, which is identical to a contusion, but without damaging associated non-vascular tissue by trauma (Harris & Gelfand, 1995). Valmyre, in 1924, stated that the intensity of the ecchymosis from cupping was observed between one to four centimetres (Valmyre, 1924). In his sequel letter in the *BMJ*, he affirms that this had been verified by post-mortems on cases who had cupping done before their death. The primarily dark colour of a contusion is because of the discharge of RBC's into the extravascular tissue. The leakage of fluids and blood into the tissue generates an inflammatory response (Takamiya et al., 2005). Neutrophils are the first reactant cells to appear in the region approximately within three to six hours; however, neutrophils, for the most part, do not hold nor create heme oxygenase-1 (Langlois, 2007). Backdrop appearance of heme oxygenase-1, and the frailer constitutive shape of heme oxygenase-2, is established in merely little quantities inside the subdermal and dermal tissues. Approximately by six hours, there is a rise in the concentration of heme oxygenase-1, which is directly associated

with the influx and rising concentration of phagocytes. The concentrations of HO-1 hit the highest points in around one to three days, then gradually reduce. Levels of heme oxygenase-1 are still amplified over basic levels even seven days subsequent to the commencement of the contusion (Langlois et al., 2015). Biliverdin from heme gives the contusion a greenish colour, and the alteration of biliverdin to bilirubin is the basis for the yellow colouration in a bruise when time passes (Langlois, 2007). The idea of DC is uncomplicated; negative pressure is applied locally above a part of the skin, which is maintained for five to ten minutes, or further, subsequently provoking a region of purpura, petechiae or ecchymosis (Tham et al., 2006). Dry cupping draws the skin inside the cup with no lacerations, whereas in bleeding cupping, the incisions are made to the skin so that blood is extracted into the cup (Kim et al., 2011). Though cupping has been a well-known healing method for hundreds of years and has been employed by people of different religions, societies and cultures, its exact method of action, the concept behind applying cups on certain points and how it works in the management of a variety of diseases, is not well defined (Ghods et al., 2016). In recent times, the importance of cupping has reappeared, and consequently, numerous research projects have started to explore its mechanism of action, promoting, emphasising and supporting cupping therapy (Rozenfeld & Kalichman, 2016). The foremost target of conventional physicians or doctors of allopathic medicines is based principally on identifying the biomedical source of the ailments, whereas the practitioners of traditional medicine or CAM are always looking for a holistic approach to address the problem (Madamombe, 2006).

Health Conditions and Proven Results of Cupping Therapy

Many reviews and research articles proposed that cupping therapy might be valuable for a range of health conditions, principally acne (Cao et al., 2013; Chen et al., 1993; Hong & Wu, 2013; Pan, 2005; Xu et al., 2013), shingles, Bell's palsy (facial weakness or facial palsy) and cervical spondylosis (Cao et al., 2012). Hijama wet cupping therapy was proven to be quite useful on liver enzymes; the advantages of lifestyle alterations are well exhibited by it. Several studies have revealed that enduring modifications in lifestyle encourage weight loss and make the hepatic enzymes and histological results better in non-alcoholic fatty liver disease (Harrison & Day, 2007; Nseir et al., 2014). Research also revealed that iron chelation treatment and Hijama wet cupping therapy could be useful in patients with a mild iron surplus. El-Shanshory chose 40 children with thalassaemia and segregated them into two sets: 20 cases received ICT plus hijama, and 20 patients obtained iron chelation treatment as the control set. The investigators established that wet cupping therapy could considerably reduce the iron surplus, reduce oxidative stress and enhance the effects of iron chelation therapy. Hence, one potential means of the healing effects of wet cupping is eliminating iron surplus in the interstitial fluid (El-Shanshory et al., 2018). Researchers observed that cupping could efficiently reduce systolic blood pressure and hence can be recommended in hypertensive patients (Aleyeidi et al., 2015; Al-Tabakha et al., 2018; Zarei et al., 2016). Jin et al. stated that cupping along with acupuncture can manage patients with herpes zoster and alleviate the pain of postherpetic neuralgia. It is specified that the wet cupping technique had established a 100% total effectiveness rate in the management of chronic urticaria, while in acne vulgaris, a 91% cure rate has been observed, particularly nodulocystic type, and just 22% in dermatitis (Unlu & Türsen, 2019).

Immune System and Cupping Therapy

Cupping appears to increase people's adaptive and innate immunity. Particularly, clinical facts propose that cupping transforms the immune reaction in humans specifically by influencing the network of cytokines. One study specifically gives a hypothetical basis for the action of cupping (Bondok, 2007). The pressure provoked by cupping causes the tissue underneath the suction cup to bulge, enlarge and become distended with interstitial and filtered fluids, consisting of CPS (causative pathological substances). This pressure (induced by suction) originates the incidents of NO production, re-establishes homeostasis, causes immediate excessive flow of blood in the blood vessels supplying any part of the body and enhances capillary and lymphatic flow (Mahmoud, 2013). This regional enhancement of circulation would be helpful for alleviating the pain. Considering the effects of the heme oxygenase–bilirubin–carbon monoxide system activation, it could be believed that the confined effect of the ecchymosis by means of CT would have an antioxidant, anti-inflammatory and pain-inhibiting outcome in the regional tissues, ensuing in an ultimate reduction of any confined inflammation, and amplification in mitochondrial production of new living cells, tissues and blood vessels in addition to a reduction of regional pain. This could ultimately lead to minimum healing time for injuries, wounds or strains contingent on the timing and site of the cupping. This may be the method of action behind a reduced sensation of pain, which has been observed in the clinical study of the effects of cupping therapy on musculoskeletal pain (Lowe, 2017). The pain that lasts for more than three to six months is termed chronic pain. It may occur due to any inflammation, damage in nerves or body tissues and may be due to any incident of the past. Numerous animal and human research studies have been performed to demonstrate the association between pain and the immune system; persistent and prolonged pain can affect the functions of the immune system (Totsch & Sorge, 2017). Cupping therapy assists the human immune system by working on the mononuclear phagocytic or reticuloendothelial system by helping it to work against the attacking microbes. The practitioners of cupping believe that the entire course of action makes the human immune system stronger, consequently supporting the body's optimum performance. This upshot on the immunity accelerates healing in patients afflicted by various ailments. It may be a solution for misery faced in numerous ailments exhibited by pain. Evaluation of the literature for CT showed that it could alleviate the pain caused by herpes zoster, lumbar disc herniation, cervical spondylosis (Cao et al., 2012; Cramer et al., 2011; Kim et al., 2018; Wan, 2007), acute gouty arthritis (Zhang et al., 2010), brachialgia, paraesthetica nocturna (Lüdtke et al., 2006), rheumatoid arthritis (Ahmed et al., 2005), CTS (Michalsen et al., 2009; Mohammadi et al., 2019), fibromyalgia (Cao et al., 2011; Cao et al., 2010; Jang et al., 2010), constant pain in the lower region of the back (Cao et al., 2014; Farhadi et al., 2009; Moura et al., 2018), persistent non-specific neck pain, (Cramer et al., 2011; Kim et al., 2018), persistent OA of the knee (Jahangir et al., 2013; Teut et al., 2012), acute tic douloureux (Zhang, 1997), migraine or other types of headache (Ahmadi et al. 2008). Cupping also aids in the management of allergy and all its associated symptoms, i.e. hives, urticaria, rhinitis. The IgE and histamine play major parts in the pathogenesis of allergic diseases, and cupping can decrease raised plasma IgE, thus inhibiting the penetrability of blood vessels and discharge of cellular transmitters, which may reduce symptoms. A study considered that cupping originates auto hemolysis, making substances similar to histamine and as a consequence making the activity of tissues, organs and the immune system stronger (Xiao et al., 2020; Chen and Li, 2004) (Table 4.1).

Table 4.1 Cupping Therapy and Its Proven Effects on Specific Ailments

Medical conditions	*Type of cupping*	*Outcomes after cupping*	*References*
Psoriasis	Wet cupping	Two days after the first hijama wet cupping therapy session, lesions began to vanish and decreased both in quantity and volume. The patient persisted for further two sessions, and over 90% of the ailment had gone, and no pruritis is sensed at any place on the skin.	(Malik et al. 2015)
Non-alcoholic fatty liver disease	Wet cupping	A study demonstrated a considerable improvement in AST and ALT serum levels in the group managed by wet cupping therapy versus the control group. Khodadoostan et al. also assessed the outcome of bloodletting. The researchers assumed that bloodletting decreases hepatic cell damage and makes liver histology and enzymes better. Moreover, wet cupping can efficiently reduce the levels of low-density lipoprotein and cholesterol, thus preventing CVD.	(Bashiri et al., 2020; Khodadoostan et al., 2017)
Knee osteoarthritis	Pulsatile dry cupping, wet cupping	The study by Jahangir et al. established cupping to be an excellent pain reliever and anti-inflammatory treatment modality with efficiency superior to acetaminophen. The subjects who have had cupping therapy demonstrated healthier outcomes in expressions of oedema, morning stiffness, pain, tenderness, crackling or rattling sounds and disability in a movement when contrasted with those on acetaminophen. Therefore, cupping can be advised for other painful diseases besides being a management line for osteoarthritis. Pulsatile and dry cupping also alleviate the symptoms of knee osteoarthritis in contrast with no treatment.	(Jahangir et al., 2013; Teut et al., 2012),

(*Continued*)

Table 4.1 (Continued) Cupping Therapy and Its Proven Effects on Specific Ailments

Medical conditions	*Type of cupping*	*Outcomes after cupping*	*References*
Myofascial pain syndrome	Dry cupping, sliding cupping, wet cupping	The cupping (dry, sliding) technique to improve the condition of chronic myofascial pain syndrome has revealed favourable results. The intention was to identify its outcome on their symptoms and their overall health status. The consequences acquired from this uncomplicated study propose that cupping could have a place in managing this ailment.	(Chirali, 2014)
Brachialgia paresthetica nocturna	Wet cupping	The outcomes were measured by noticing the change in pain intensity, lack of sensation and tingling. According to Ludtke et al., wet cupping has assisted 95% of cases of brachialgia.	(Lüdtke et al., 2006)
Acute trigeminal neuralgia	Wet cupping, acupuncture along with cupping therapy	In TCM, cupping therapy and acupuncture proved to successfully manage acute trigeminal neuralgia.	(Z. Zhang, 1997)
Chronic back pain	Dry cupping, moving cupping, wet cupping, cupping along with acupuncture	More than 600 studies were established, including both qualitative and quantitative analysis; these research projects detected that the cases that were present in the trial group and have received hijama/ wet cupping therapy recorded considerably lower measures of disability and pain, moreover, it reduced the need to take anti-inflammatory or other analgesic drugs for chronic back pain. Consequently, it has demonstrated positive and promising outcomes in both specific and non-specific back pain.	(Cao et al., 2014; Farhadi et al., 2009; Moura et al., 2018)

(*Continued*)

Table 4.1 (Continued) Cupping Therapy and Its Proven Effects on Specific Ailments

Medical conditions	*Type of cupping*	*Outcomes after cupping*	*References*
Hypertension	Dry cupping along with wet/hijama cupping therapy	Wet cupping therapy can be utilised efficiently to decrease systolic blood pressure. Thus, if employed in combination with the allopathic antihypertensive medicines, the titration of medications can be performed without fear of any unpleasant effects, while getting the required blood pressure targets. Other studies with a larger sample size also confirmed that hijama wet cupping therapy can remarkably decrease SBP; however, DBP isn't affected much by it, confirming that cupping is efficient in managing patients with hypertension.	(Aleyeidi et al., 2015; Al-Tabakha et al., 2018; Zarei et al., 2016),
Allergic rhinitis	Acupuncture along with moving cupping	The scientific observation confirmed that acupuncture along with moving cupping on the back had affirmative effects in patients with allergic rhinitis.	(Zhang, 2010)
Cellulitis	Wet cupping along with medicines	Wet cupping along with antimicrobial therapy was administered at the site of utmost inflammation in cellulitis and more than 30 incisions were made by which 9 millilitres of blood were extracted. An instant clinical improvement and inhibition of all signs and symptoms of inflammation were observed—wet cupping aids in eliminating the microbial toxins and microorganisms from blood to outside the human body.	(Ahmed, 2011)
Herpes zoster	Acupuncture and wet cupping	Outcomes of multiple randomised controlled trials demonstrated the comparison of conventional medicines with cupping therapy and it revealed that cupping was considerably better in managing pain, lesions and postherpetic neuralgia. The combination of cupping with other modalities was proven to be more efficient than these modalities alone.	(Cao et al., 2010; Jin et al., 2008),

(*Continued*)

Table 4.1 (Continued) Cupping Therapy and Its Proven Effects on Specific Ailments

Medical conditions	*Type of cupping*	*Outcomes after cupping*	*References*
Carpal tunnel syndrome	Moving cupping and wet cupping	A solitary method of healing considerably decreased the symptoms of CTS and the related pain in the neck, while no unfavourable incidents were detected. Researchers also established that a single session of cupping was effective in alleviating the symptoms of CTS.	(Michalsen et al., 2009; Mohammadi et al., 2019),
Asthma	Dry cupping, cupping with acupuncture, water cupping	A distinct recommendation for asthma is cupping of the region between BL-13 Feishu and Du-14 Dazhui. A number of asthmatic patients at Gansu Province were managed with water cupping on ST-15 Wuyi and BL-13 Feishu.	(Deng et al., 1989)
Facial paralysis/Bell's palsy	Acupuncture with cupping, flash cupping, plum blossom needle therapy, wet cupping	Several randomised control trials evaluated the healing outcome of cupping therapy for Bell's palsy/facial paralysis. Divergence of eyes and mouth was managed by cupping over Du-14 Dazhui, ST-4 Dicang and Taiyang extra. Several cases were managed by acupuncture and various forms of cupping at the paralysed site. There was a significant improvement in all the symptoms of disease.	(Cui & Zhang, 1989; Gao, 2010; H.-T. Li & Liu, 2005; W.-H. Li, 2005; Youbang et al., 1989)
Chronic urticaria (CU)	Dry cupping, wet cupping	Both dry and wet cupping was used to manage CU and numerous studies were conducted in favour of chronic urticaria's management by cupping therapy amongst which four studies used dry cupping. The cups were applied on acupoint DU 14, CV 8 and ST 36. The meta-analysis also revealed that wet cupping might be equally useful with antihistamines in management of CU.	(Teng & Chen, 2014; Xiao et al., 2020; Yao et al., 2019)

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Table 4.1 (Continued) Cupping Therapy and Its Proven Effects on Specific Ailments

Medical conditions	*Type of cupping*	*Outcomes after cupping*	*References*
Cervical spondyolitis	Wet cupping, moving cupping, pulsating cupping, flash cupping, sliding cupping, acupuncture with cupping	The proficiency of CT for cervical spondylosis has been proven by numerous studies, especially bleeding cupping in combination with other treatment modalities, for instance, acupuncture, massage etc. Cupping therapy reduced chronic neck pain and improved quality of life and minimised the chances of its relapse.	(Cao et al., 2012; Cramer et al., 2011; Kim et al., 2018; Wan, 2007)
Hypercholesterolemia	Wet cupping therapy	Bleeding cupping is an efficient way of lowering low-density lipoprotein in men and, therefore, may have a protective effect in case of atherosclerosis. A considerable reduction in LDL, moreover in the ratio of low-density and high-density lipoprotein, was established in the experimental group as compared to the control group.	(Niasari et al., 2007)
Acute gouty arthritis	Wet cupping along with herbal medicines	Wet cupping on a distressed area could alleviate gout pain, remove the stagnant toxic blood, and encourage blood circulation without demonstrating any severe side effects. According to a study, WCT and herbal medicines are effective for managing acute gouty arthritis and are advised to be used in clinics.	(S.-J. Zhang et al., 2010)
Fibromyalgia	Cupping with acupuncture, cupping with medicines, wet cupping therapy	Several randomised control trials showed that cupping therapy in combination with acupuncture or conventional medicine proved to be effective in reducing the pain and tenderness of fibromyalgia as compared to allopathic medicine alone. Wet cupping is believed to be more appropriate and effective management of fibromyalgia because it can inhibit interstitial fluid pressure from inflammation sites.	(Cao et al., 2011; Cao, Zhu, et al., 2010; Jang et al., 2010)

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Table 4.1 (Continued) Cupping Therapy and Its Proven Effects on Specific Ailments

Medical conditions	*Type of cupping*	*Outcomes after cupping*	*References*
Rheumatoid arthritis	Wet cupping therapy	Cupping with medicines was proven to reduce the severity of pain, DAS (disease activity score), swelling and tenderness of joints in patients with rheumatoid arthritis. Moreover, Ahmed et al. stated both wet cupping and medicines considerably reduce laboratory findings of disease, i.e. RF, CRP, ESR, SII-2R which were kept estimated for more than three months.	(Ahmed et al., 2005)
Headache	Wet cupping	In an experiment, the severity of headache and migraine was observed to be efficiently decreased by 66% after wet cupping therapy; furthermore, the patients that were managed by wet cupping confronted 12 to 13 fewer days of headache/month. Wet cupping encourages plasma clearance by removing unnecessary fluids, especially those agents responsible for causing headaches.	(Ahmadi et al., 2008)
Acne	Moving cupping, wet cupping, cupping with acupuncture, cupping with herbs, cupping with moxibustion	Lots of experimental trials have assessed the efficiency of cupping therapy for acne and all of them demonstrated significant improvement in healing rate, reduction of pain and papulopustular eruptions in contrast to with conventional medicines.	(Cao et al., 2013; Chen et al., 1993; Hong & Wu, 2013; Pan, 2005; Xu et al., 2013)

Conclusion

Cupping can keep the body in a balanced and healthy state. Various studies conducted on this therapy have shown remarkable results, especially in chronic diseases. Trials conducted on a large scale will be the foundation for representing cupping therapy's efficiency and enduring outcomes.

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Chapter 5

Do Exercise and Yoga Improve the Quality of Life?

Introduction

Quality of life (QOL) is a multidimensional and multifaceted concept that has a range of interpretations. QOL is considered by experts as 'a personal satisfaction', 'significance bestowed to life', 'being the fundamental state for happiness' and 'an adaptive capacity'. The aspects of QOL are classified into, for example, independence, mental or emotional wellbeing, physical wellbeing, interpersonal connections, physical wealth, subjective affirmation, social integration and guaranteeing essential human rights. With respect to its aspect of physical wellbeing, quality of life is a significant benefit of physical activity (PA) since PA has an impact on social integration, emotional state, material wealth and productivity. By means of physical exercise, people not only make their physical state better but also improve their self-esteem, levels of stress, working productivity, management of personal life and ultimately quality of life. In one of the studies, research participants established that physical activity meets the essentials and contributes to quality of life (increases social connections, improves moods, etc.); they went forward with the continuum to more autonomous motivation. The cycle in which physical activity increases the quality of life and increased quality of life motivates involvement in physical activity generates a positive cycle of health. The American Heart Association proposes that walking is the easiest way to begin and keep up with a healthful life (Figure 5.1) as this physical activity costs people nothing and is uncomplicated, safe and provides the body with a healthy heart (American Heart Association, 2018; Ana-Maria, 2015; Delle Fave, 2013; McCall, 1975).

Furthermore, in accordance with the American Heart Association, average exercise or physical activity performed for at least half an hour per day has numerous verified benefits for human health, which include weight control, a boost in levels of

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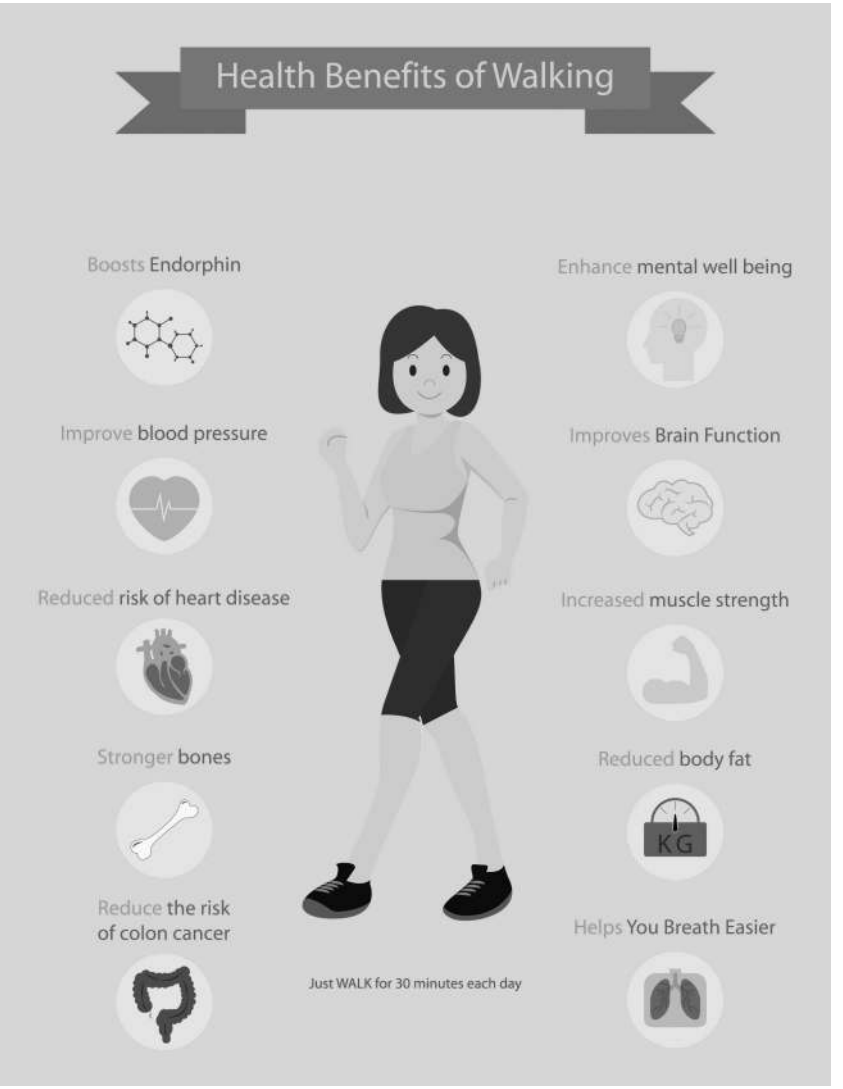

Figure 5.1 Health benefits of walking.

energy, help in the management of stress, decreased tension, depression and anxiety, enhanced circulation of blood and decreased risk of cardiac diseases, help in the management of blood glucose, blood cholesterol and blood pressure, preventing the ageing process and loss of bone, encouraging optimism and enthusiasm, assisting people in having a quick and sound sleep, decreasing the risk of coronary heart disease by 30 to 40% in women, preventing the risk of developing cardiac ailments and stroke in later parts of life (due to an unhealthy or sedentary lifestyle) and also prevention of lots of chronic ailments related to the ageing process while maintaining quality of life (American Heart Association, 2018; American Heart Association et al., 2006; Ana-Maria, 2015).

Moreover, the immune system is also extremely reactive to exercise, though exercise immunology is considered a somewhat new discipline of scientific attempt with around 90% of studies issued after the year 1990 (van Dijk & Matson, 2016), with the duration and level demonstrating the extent of physiological stress executed by the load of work. The most primitive studies regarding exercise immunology emphasised changes persuaded by exercise in fundamental function and count of immune cells (Shephard, 2010). With the passage of time, these short-term exercises prompted enhancements in particular subsets of lymphocytes that increase immunosurveillance and inhibit inflammation, which may be of specific clinical significance for diseased and obese people (Evans et al., 2015; Ferrandi et al., 2018; Viana et al., 2014). Generally, acute physical activity or exercise is now regarded as a significant adjuvant for the immune system to encourage the continuing leukocytes exchange between the tissues and circulation (Adams et al., 2011). An auxiliary advantage is that acute exercise may function as an uncomplicated strategy to enhance the blood section of extremely cytotoxic subsets of natural killer cells and T cells that can be collected for clinical use. Meanwhile, moderate exercise metabolically encourages acute but small advancements in interleukin-6 that directly apply anti-inflammatory effects, making the metabolism of lipid and glucose better with the passage of time. Altogether, the finest proof bolsters that excessive workloads of exercise training, competition events and the related psychological, metabolic and physiological stress are associated with muscle injury, immune dysfunction, oxidative stress and inflammation (Nieman & Wentz, 2019) (Figure 5.2).

Nowadays, people are also paying special attention to mind-body therapies since the awareness of complementary and alternative medicinal approaches is enhancing. People are embracing it as part of their lives; one of the examples of commonly practised mind-body therapy includes yoga, which is an ancient regimen invented to bring health and harmony to the spiritual, mental, physical and emotional elements of the person. Certainly, in a national survey in 2007 on community-living adults conducted in the United States, almost 19% stated that they had employed at least one therapy of mind and body in the previous year, and estimates are even greater among the clinical population (Barnes et al., 2008). Yoga is one of the therapies amongst them; it is a combined practice of mind and body, initiated around 5000 BC in ancient India. Since that time, it has been used to encourage wellbeing and health across a number of disorders. The term 'yoga' originates from Sanskrit and may be interpreted as 'conjunction' or 'union', necessitating the concept of uniting mind, body and spirit (Feuerstein, 2011). However, in western countries, yoga is principally employed as a practice for relaxation and enjoyment; it is progressively acquiring interest as a clinical intervention (Falkenberg et al., 2018). Ashtanga yoga, discussed by Maharishi Patañjali, is often represented figuratively as a tree and consists of eight 'limbs' or facets (Figure 5.3), i.e. universal morality (*yama*), personal ethics (*niyama*), bodily postures (*asana*), regulation of breath (*pranayama*), modulation of the senses (*pratyahara*), concentration (*dharana*), meditation (*dhyana*) and perfect happiness (*samadhi*) (Iyengar, 2001). Each extremity is associated with the whole, identical to the limbs of the human body that are all attached. If anyone tugs the body by means of the leg, the remaining body will follow automatically. Similarly, when anybody pulls one of the eight yoga limbs, the remaining will automatically appear. They are not phases to be accomplished in sequence (Damodaran et al., 2002). Indeed, yoga did not principally develop as a system of physical activities but as a system of healing as well (Desikachar et al., 2005). This system of healing is founded on the belief that humankind is holistic, distinctive and an interrelated

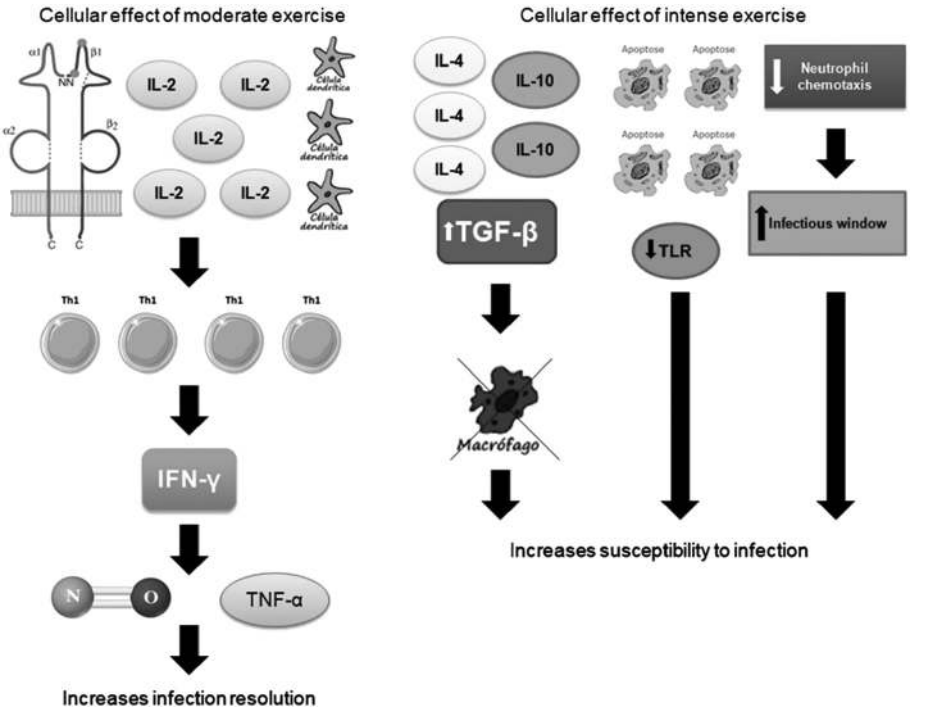

Figure 5.2 Effects of exercise on the immune system. (Source: illustration acquired from 'Physical Exercise as a Tool to Help the Immune System against COVID-19: An Integrative Review of the Current Literature' (2020) by da Silveira et al. Springer Nature BV.)

body; yoga can give authority to an individual to become active and take responsibility for their own healing; moreover, the state of mind of a person is fundamental in this healing course (Desikachar et al., 2005).

A persistently rising interest in research verifications validates the belief that particular techniques of yoga may improve mental and physical health by means of down-regulating the SNS (sympathetic nervous system) and HPA (hypothalamus pituitary adrenal axis). The SNS and HPA axis is stimulated as a reaction to psychological or physical need (stressor), giving rise to a cascade of psychological, behavioural and physiologic outcomes, principally as an outcome of the catecholamines and cortisol release. This reaction causes the energy mobilisation required to fight with the stressor by means of the classic 'fight or flight' response. With the passage of time, the continuous state of hypervigilance ensuing from the recurrent firing of the sympathetic nervous system and hypothalamus-pituitary-adrenal axis can cause the dysregulation of the system and eventually diseases such as cardiovascular ailments, diabetes, depression, obesity, substance abuse and autoimmunity (McEwen, 2000; Sterling, 2004).

Historical Aspects of Yoga

Rigveda, one of the first books of humankind, talks about yogic meditation, while Yajurveda (one of the four Vedas) encourages people to practice yoga for increasing

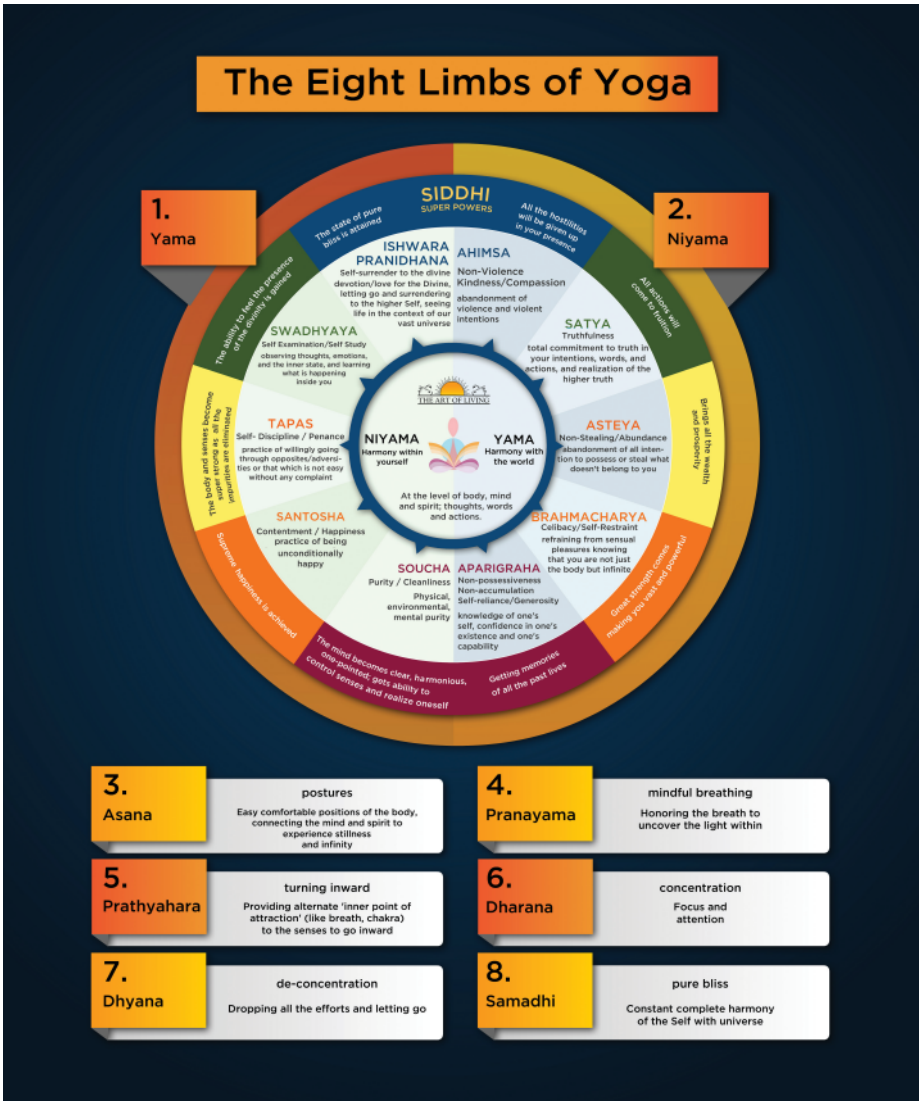

Figure 5.3 Patañjali's eight limbs of yoga.

mental health, prosperity and physical strength. *Gheranda Samhita* (a Sanskrit textbook of yoga) mentioned there were around 84 lakh *asanas* (physical exercises), among which 16,000 were fine and merely around 300 were well-liked. One of the classic Sanskrit handbooks, *Hatha Yoga Pradipika*, inscribed by Svatmarama, again classified all *asanas* into four basic classes: *vadrasana*, *sinhasana*, *padmasana* and *sidhyasana*. Apart from this, *asanas* may be of two kinds: *shasthyasana* (to acquire a healthy body) and *dhyanasana* (a position that frees the spinal cord and shifts the gravity centre to other areas such as ribs). Generally, yoga is perceived to be a *pranayama* (breathing exercises) and *asanas* (physical exercises) programme in accordance with the archaeological proof (Raj, 1995) where it appeared in the ancient Hindu texts (*Vedanta* or *Upanishads*). It is stated in the classic Indian book

Mahabharata and also discussed in the *Bhagavad Gita*. Yoga was actually organised in the yoga sutras by sage Patañjali, who described the aim of yoga as an understanding of the real 'self'. Yoga, as taught and practised in India, was launched into the western regions in the 19th century with the interpretation of fundamental yogic literature. Swami Vivekananda was the one who brought yoga to the United States of America in 1893, subsequent to the World Parliament of Religions in Chicago. He extensively gave lectures on the yoga practice, authored several books and also established the Vedanta Society. Afterwards, yoga was promoted in the west by many teachers who had taken their education from eastern regions (primarily India); a number of them moved to America at the beginning of the 20th century. Several kinds of yoga were discovered and taught in the 20th century. Many books helped in the growth of a community for practising yoga in the United States of America. In the 1950s, 'an intensely trendy explosion of interest in hatha yoga' took place in the United States of America and in the same decade, yoga expanded by means of beauty and health salons. During the era of the 1950s to 1960s, various significant books and manuscripts were published on techniques of yoga and subsequently, in the 1970s, yoga therapy developed swiftly, with the establishment of many professional organisations and yoga centres. Yoga particularly became famous among supporters of new-age concepts (Sengupta, 2012).

Impact of Yoga on Human Health

Regularly practising yoga encourages flexibility, endurance and strength and facilitates remarkable self-control, compassion and friendliness characteristics while bringing on a sense of wellbeing and calmness (Collins, 1998; McCall, 2007). Continuous yoga practice also gives rise to significant outcomes, i.e. liveliness with actual enjoyment, modifications in the outlook of life, better energy sense and self-awareness (Atkinson & Permuth-Levine, 2009; Desikachar et al., 2005; Mehta et al., 1990); yoga practice creates a physiological condition contrary to that of the fight-or-flight response since yoga is a kind of MBI (mind-body intervention) that includes a blend of physical activity and an internally controlled emphasis on mindful awareness of the energy, breath and self (Collins, 1998). Nowadays, lots of people recognise yoga only as physical exercises (*asanas*); however, *asana* is merely one of the several tools utilised for treating the person; of 196 sutras, only three refer to the *asana* and the rest of the literature talks about the other yoga components including modification in diet and lifestyle, meditation, utilisation of sound, visualisation and conscious breathing among several other (Desikachar et al., 2005). Various research studies reveal that yoga inhibits blood glucose (Gokal et al., 2007; Khatri et al., 2007), salivary cortisol (Michalsen et al., 2005; West et al., 2004), as well as levels of plasma rennin and 24-hour levels of epinephrine and norepinephrine (Selvamurthy et al., 1998). Yoga considerably reduces diastolic blood pressure, systolic blood pressure and heart rate (Selvamurthy et al., 1998; Sengupta, 2012). Shapiro et al. (2007) observed a considerable decrease in cardiac rate fluctuation and indication of SNS (sympathetic nervous system) stimulation in patients with depression after almost two months of intervention with yoga. In spite of the pathophysiologic route, yoga has been demonstrated to have instant psychological outcomes such as enhancing the feelings of spiritual, social and emotional wellbeing (Moadel et al., 2007) and inhibiting anxiety (Gupta et al., 2006; Michalsen et al., 2005; Telles et al., 2006;

West et al., 2004). A number of studies have been carried out that analysed yoga's impact on particular health conditions, including cancer (Bower et al., 2005), metabolic syndrome (Innes et al., 2005), anxiety (Kirkwood et al., 2005), cardiovascular diseases (Raub, 2002) and diabetes (Upadhyay et al., 2008). The most extensively researched and practised hatha yoga focuses on two principal aspects, i.e. breathing exercises (*pranayama*) and physical exercises (*asanas*) (Raj, 1995). Hatha yoga increases the ability of the body by means of utilising a series of breathing methods (*pranayama*) and physical postures or exercises (*asanas*). The ways of breathing in hatha yoga emphasise exhalation, retention of breath and conscious extension of inhalation. It is by means of integrating concentration, breath and the physical body while carrying out the movements and postures which ultimately clear the obstructions in the body's energy pathways and make it more balanced. Though there are a number of ways of doing hatha yoga, the most common of them are Iyengar yoga styles. Iyengar yoga focuses more on standing postures to develop stamina, strength, concentration, body alignment and stability. Props are used to make learning easy and to amend instruction and poses, based on how to apply yoga to alleviate different diseases and stressors (Woodyard, 2011). The principal aspects of hatha yoga are discussed in the following sections.

Pranayama

The Sanskrit word '*pranayama*' is made up of two words, i.e. '*prana*' which means vital energy/life force and '*ayama*', meaning control/regulation (Nivethitha et al., 2016). It is the yogic breathing skill, comprising the intentional alterations of the breathing method, such as breathing from alternate nostrils, deep/slow breathing, retention/holding of breath and rapid diaphragmatic breathing, which are typically performed in a sitting position (Joshi, 2006). Iyengar states that emotional exhilaration influences the respiratory rate, while intentional control of breathing regulates emotional exhilaration. Since the purpose of yoga is to still and regulate the mind, initially, the yogi comprehends *pranayama* to gain control of breath (Iyengar, 1979) (yoga pose). *Pranayama* is best executed seated (Figure 5.4) with a pile of blankets or a block placed under the hips at the same time, keeping the back erect from the bottom of the spine to the neck (Desikachar, 1999).

Iyenger advises that during *pranayama*, the eyes should be closed so that the ideas cannot wander. Moreover, both of the hands should be placed on the lower limbs, and the hands' palms should be facing upward to acquire positive energy; leaning down on the back of the spine after performing *pranayama* is also recommended by Iyengar. This posture is called 'corpse pose' or *shavasana* (Figure 5.5), and it allows the body and mind to be reinstated after a number of breathing methods and postures. Iyenger states that the person who is performing *shavasana* after *pranayama* should be relaxed in this posture, but the person shouldn't be in a state of sleep (Iyengar 2013).

Pranayama consists of four significant breathing aspects, which include inhalation (*puraka*), exhalation (*recaka*), retention of breath internally (*antah kumbhaka*) and retention of breath externally (*bahih kumbhaka*) (Nivethitha et al., 2016). In accordance with Patañjali's yoga sutra (one of the most reliable books of yoga in India), among the eight limbs of yoga, *pranayama* is the fourth one (Patañjali & Hartranft, 2003). *Pranayama* has shown several favourable health outcomes,

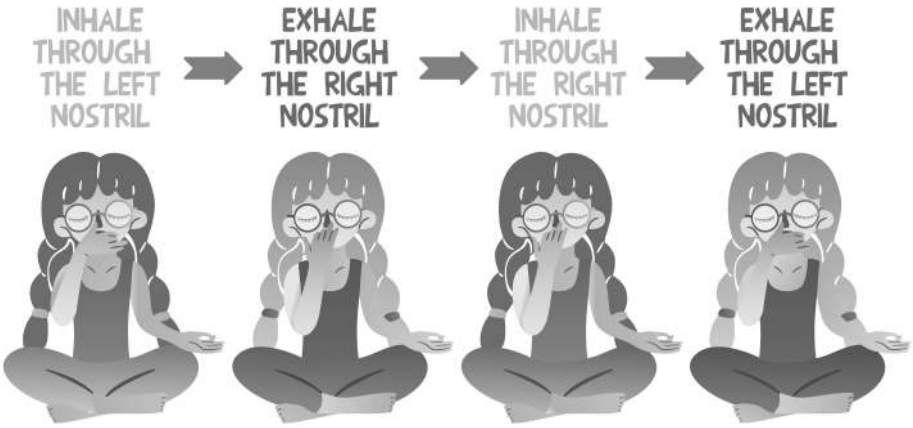

Figure 5.4 *Pranayama* (breathing from alternate nostrils).

Figure 5.5 *Shavasana* or corpse pose.

including improved pulmonary function (Saxena & Saxena, 2009), increased cognition (Sharma et al., 2014), beneficial effects on the cardiovascular system and stress relief (Sharma et al., 2013). Though short-lived outcomes of *pranayama* are on the pulmonary system, its long-standing effects have been demonstrated to make the conditions of the endocrine system, nervous system and circulatory system better and assist in preserving the functions and homeostasis of internal organs (Brown & Gerbarg, 2005a; Madanmohan et al., 2005).

The process included in *pranayama* is for the regulation of breathing, while the deep breathing techniques help in strengthening the intercostal and diaphragmatic muscles' efficiency with the provision of better ventilation in minimum energy usage. The long-standing outcome of the practice gives rise to decreased pulmonary rate and enhanced tidal volume by inhibiting residual volume. Enhanced residual volume in the respiratory tract is one of the harmful factors that have the tendency to enhance the breathing work and fatigue in healthy persons throughout physical execution. Contrary to other physical workouts, *pranayama* can be done regularly in the early morning after taking a bath and by maintaining a fasting state. Ultimately, the aim of *pranayama* is to increase the parasympathetic reaction. Performing it in a room with sunlight or by sitting outside in the sun is advised. The persons who started doing *pranayama* can feel the energy in their body; even on the very first day, the body feels calm and composed (Madanmohan et al., 2005; Shetty, 2016; Yadav & Das, 2001).

Asanas *Including Sun Salutation (*Suryanamaskar*)*

Yoga therapy includes instruction in yogic teachings and practices to prevent or alleviate spiritual, physiological, structural and emotional suffering or pain. Yogic practices increase flexibility and strength of muscles and body, improve cardiovascular and pulmonary function, encourage recovery from addiction, decrease chronic pain, stress, depression and anxiety, improve patterns of sleep and increase the quality of life and overall wellbeing (Woodyard, 2011). *Suryanamaskar* or sun salutation, also known as sun adoration for longevity, efficiency and health, is a fragment of traditional Indian yogic practices. It includes *upasana* (such as rituals), *pranayama* and *asana*. *Suryanamaskar* is carried out as a series of events accompanied by a particular pattern of breathing. Each cycle of sun salutation comprises ten steps consecutively executed one after the other. The cycle starts with *pranamasana* or *stithi*, the posture of prayer, followed by a sequence of steps, i.e. (1) *hastauttanasana* (raised arm pose), (2) *padahastasana* (standing forward bending pose), (3) *ashwa sanchalasana* (equestrian pose), (4) *parvatasana* (mountain pose), (5) *ashtanga namaskara* (knees-chest-chin pose), (6) *bhujangasana* (cobra pose), (7) again *parvatasana* (mountain pose), (8) *ashwa sanchalasana* (equestrian pose), (9) *padahastasana* (standing forward bending pose), (10) *hastauttanasana* (raised arm pose) and coming back to standing position. Each of these *asanas* (body postures) has separate benefits for health (Bhutkar et al., 2011).

Sun salutation is a set of *asanas* that require a specific breathing pattern. It reinvigorates all of the body's cells, providing mental peace, physical strength and flexibility (Satyānanda, 2009). To the greatest extent feasible, these postures (*asanas*) include alternating backward and forward bending, as well as deep inhalation and exhalation. These exercises contract and stretch the entire musculoskeletal system in a methodical manner, simultaneously giving additional strength and flexibility (Vaibhav et al., 2016). The training of yoga enhances the flexibility in muscles of the body, particularly the back, buttock, leg and chest (Sinha et al., 2004). Practising *asanas* daily can also assist a person in losing excess fat in the body. It relaxes the joints and provides tonicity to the internal organs and body muscles. It maintains equilibrium in the endocrine, pulmonary, reproductive and circulatory systems. The postures and moves of the *asana* assist all the internal organs in the human body to function in a good way. It also assists in overcoming the situation of insomnia since it provides relaxation to the body and mind, eliminates lethargy and enhances alertness. It also aids in controlling the flow of menstrual cycles and easing the suffering of childbirth. Sun salutation stimulates the *surya nadi*, which increases the levels of energy in the body (Vaibhav et al., 2016) (Figure 5.6).

Effects of Exercise and Yoga on PCOS

In reproductive women, the most frequently seen hormonal disease is polycystic ovarian disease, affecting around 5 to 15% of females as early as in their 20s (Franks, 1995; March et al., 2010; Welt & Carmina, 2013). Since the precise causes of the disease are unidentified, it is recognised by depending upon the agreed criteria and the elimination of other endocrine diseases, with the most frequently used being the Rotterdam criteria for the diagnosis of PCOS (Shele et al., 2020). Polycystic ovarian syndrome is distinguished by anovulation or oligoovulation, hirsutism,

Figure 5.6 Steps of sun salutation or *suryanamaskar*.

hyperandrogenism, acne, subfertility, infrequent cycles of menstruation and alopecia (Franks, 1995; Raj et al., 1978). Along with the reproductive and endocrine effects, polycystic ovarian syndrome also affects psychological and cardio-metabolic health over the lifespan (Shele et al., 2020; Teede et al., 2010; Welt & Carmina, 2013).

Women with polycystic ovarian disease are more likely to get type 2 diabetes mellitus, obesity, nonalcoholic fatty liver disease and cardiovascular disorders, besides having an enhanced risk of developing disorders of mood, anxiety and depression. The ovaries of women with PCOS are triggered to synthesise excessive quantities of androgens; this may be due to the hyperstimulation caused by the LH or the intrinsic impairment of steroid synthesis (Shele et al., 2020).

Physical workout is a segment of lifestyle management for patients with polycystic ovarian syndrome. Intensive aerobic exercise, particularly when practised regularly for a more extended period and in combination with monitoring of cardiac rate and/or VO2max, can make the measures of insulin sensitivity better. Levels of androgen are more likely to get better with strength or resistance training; the influence of yoga on androgens and sensitivity of insulin emerges to be promising and needs further research (Shele et al., 2020). In one of the randomised controlled trials, yoga was contrasted with typical exercise in girls of adolescent age suffering from polycystic ovarian syndrome; around three months of intervention with supervision included 90 sessions of approximately 60 minutes consisting of various asanas (body postures), sun salutation, meditation, relaxation and pranayama in the yoga group. In contrast, the group of conventional exercises included standing, walking, supine and sitting exercises with no breathing techniques or concepts of yoga.

Outcomes revealed that girls in the yoga group had decreased levels of HOMA-IR (insulin resistance index), testosterone, fasting insulin, luteinising hormone and anti-mullerian hormone after intervention (Nidhi et al., 2012).

Effects of Exercise and Yoga on Respiratory Tract Disorders

Breathing techniques in yoga have also been established to be beneficial in enhancing the function of the lungs in diseases with respiratory suffering such as bronchial asthma and chronic obstructive pulmonary disorders (Umesh et al., 2021). Regular exercise of average intensity has already been related to a decrease in infections of the respiratory tract contrasted to being lazy and lethargic. However, intensive physical exercise prior to or throughout the illness, such as COVID-19 or influenza, can precipitate severe disease because of the modifications in the immune system (da Silveira et al., 2021).

Impact of Exercise and Yoga on the Immune System

Physical workout is regarded as one of the most important aspects of a healthy lifestyle. A possible advantage of physical exercise in lowering infectious diseases, particularly viral diseases, has been postulated, besides the functions associated with regulating the excess weight of the body, systemic inflammation and persistent non-infectious diseases (Laddu et al., 2021).

Physical activity, in both its acute and long-term manifestations, has a significant impact on the immune system (Leandro et al., 2007; Pedersen & Hoffman-Goetz, 2000). According to studies, the immunological response to exercise is regulated by characteristics such as intensity, regularity, duration and sort of effort exerted (Laddu et al., 2021; Simpson & Katsanis, 2020). Physical activities of moderate intensity enhance cellular immunity, whereas extended or high-intensity workouts without adequate rest decrease cellular immunity, making individuals more susceptible to communicable diseases (Leandro et al., 2007; Pedersen & Hoffman-Goetz, 2000).

Lack of physical exercise, according to Luzi and Radaelli (2020), is a significant component in obese individuals as it affects the immunological responses to microbial pathogens, influencing everything from macrophage activation to pro-inflammatory cytokine reduction. Physical activity, on the other hand, is beneficial to both metabolic and immunological health, lowering the risk of infection problems. Hence performing physical exercise on a regular basis emerges as a measure of prevention in the protection of the host against viral infectious diseases since physical activity is demonstrated to be a non-medicinal and immunostimulatory intervention, acquiring constructive immunomodulation by means of light to moderate exercises (Luzi & Radaelli, 2020).

Secretions of stress hormones and inflammatory reactions are reduced during daily physical activity; however, natural killer cells, monocytes, lymphocytes and primitive B-lymphocytes are at high levels. Consequently, there is an increase in immune vigilance as well as a decrease in the systemic process of inflammation, both of which are factors that support the idea that physical activity, if performed daily, can make the immune system function in a better way while also preventing

pulmonary diseases and thus helping to protect against infections like COVID-19 (Nieman, 2020). In accordance with the research, yoga appears to counteract the harmful effects of stress on the immune system by raising levels of immunoglobulin A and natural killer cells. Yoga has been established to inhibit inflammatory markers such as C-reactive protein along with inflammatory cytokines, i.e. lymphocytes 1B and interleukin-6 (Ross & Thomas, 2010).

Impact of Yoga on COVID-19

The pandemic of coronavirus disease 2019 turned out to be a crucial health challenge for the whole world, particularly for the health care division. The current strategies of health care have focused principally on either the infectious agent or the environmental components. Though, the efforts for enhancing the immunity of the host are significant from the perspective of public health to down-regulate the agent's potency and preclude the dissemination of infection. Though vaccines against COVID-19 disease can enhance the specific host immunity (Stebbing et al., 2020), nonspecific methods for improving the overall immunity of the host are the need of the hour. Fascinatingly, yoga therapy stresses the regulation of host factors, i.e. modulation and control of the factors for lifestyle (Umesh et al., 2021). The immunity of the host is downregulated because of changing patterns of lifestyle such as intake of unhealthy food, addictions, stress, an enhanced load of work, physical inactivity, an improper cycle of sleep and wakefulness (Segerstrom & Miller, 2004; Bhargav et al., 2010).

Yoga has been contemplated as one of the activities that can be carried out at home to enhance mental wellbeing throughout the pandemic duration (Puyat et al., 2020). Nagendra et al. focused on the body's homeostasis in addition to the mind and presented the logical relevance of five sheaths of subsistence (*pancha-koshas*), and misinterpretation of the subject (*viparyaya vritti*) of mental disorders (*pancha vrittis* of Patañjali) and the opposite mental approach advised in the literature of yoga (*pratipaksha bhavana*) in the current context, besides the pieces of evidence proposing the role of yoga as complementary management in decreasing the severity of inflammation and infections. (Nagendra, 2020). Many randomised control trials show the effectiveness of yoga in controlling inflammatory indicators. One of the systematic reviews of around 15 randomised controlled trials showed that the yoga practice considerably reduced pro-inflammatory markers, i.e. TNF-α, IL-1β and IL-6, and moreover enhanced the anti-inflammatory indicators such as IL-12 and IL-10 (Falkenberg et al., 2018). Furthermore, Davidson et al. showed a rise in antibody titers in reaction to the influenza vaccine in the individuals who performed eight weeks of meditation programme contrasted with the non-meditating controls (Davidson et al., 2003). Research has also revealed more significant levels of circulating NK cells, CD3+, B-lymphocytes, CD8+ and CD4– cells in the practitioners of yoga and meditators in contrast with non-practitioners (Umesh et al., 2021).

Yoga Helps in Alleviating Stress

Clinical and experimental research shows that yoga decreases stress (Chong et al., 2011). Recent literature about the effects of yoga on stress documented that around 25

out of 35 articles documented a considerable drop in levels of anxiety after the intervention of yoga (Li & Goldsmith, 2012). Psychological mechanisms that have been advised as methods by means of which yoga mitigates stress involve a rise in constructive attitudes towards stress (Malathi & Damodaran, 1999; Taylor, 2003; Woodyard, 2011), mindfulness (Brown & Ryan, 2003; Chiesa & Serretti, 2009; Evans et al., 2015), coping mechanisms (Heilbronn, 1992; Rizzolo et al., 2011; Kinser et al., 2013), calmness (Brown & Gerbarg, 2005b; Sherman et al., 2013), compassion (Braun et al., 2012), self-awareness (Arora & Bhattacharjee, 2008), spirituality (Evans et al., 2011; Moadel et al., 2007) and appraisal of control (Bonura, 2008). Numerous researchers propose that mindfulness is a strong association between reducing stress and practising yoga (Dunn, 2008). The literature is growing regarding the prospective mediating effects of the endocrine and inflammatory reactions, the autonomic nervous system and the hypothalamus-pituitary-adrenal axis (Riley & Park, 2015).

Yoga has been related to greater mindfulness levels; Brisbon and Lowery (2011) established that practitioners of advanced yoga had greater levels of mindfulness and minimum stress levels contrasted with yogis who are beginners. The biological mechanisms that are proposed as means by which yoga may inhibit stress include the hypothalamus-pituitary-adrenal axis, the autonomic nervous system (Riley & Park, 2015), gene expression (Black et al., 2013), the peripheral nervous system, including GABA (Streeter et al., 2012), endocrine and inflammatory reactions (Kiecolt-Glaser et al., 2010; Yadav et al., 2012), release of nitric oxide and endothelial functions (Dunn, 2008; Michalsen et al., 2005), endogenous opiates and cannabinoids (Michalsen et al., 2005) and activity of the limbic system (Riley, 2004).

Conclusion

There has been a considerable rise in the number of research studies on physical activity (including yoga and exercise) and its effects on the human immune system. The accessible proof demonstrates that physical exercise has considerable regulatory effects on the activities of immune cells and probably on functions of the immune system. These effects are controlled by a variety of factors, including the release of pro-inflammatory cytokines persuaded by exercise, hemodynamic outcomes and long-established stress hormones. They are giving rise to redistribution of cells while yoga is frequently utilised as a management strategy for stress in diverse populations. Sun salutation or *suryanamaskar* does not need any gadgets or equipment, a limited place is adequate to execute these *asanas* and merely a small amount of time is required to execute some cycle numbers. In general, yoga, walking, resistance training, aerobic exercises and all other forms of mild to moderate physical activities which improve the composition, endurance, muscle strength, hormones and mental activity of the human body are supposed to be the indispensable constituent of a fitness process.

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Chapter 6

Psycho-Immunomodulatory Benefits of Aromatherapy

Introduction

Aromatherapy or essential oil (EO) therapy is an organic and botanical way of treating an individual's body, mind and soul. It combines two words, i.e. aroma, which symbolises smell or fragrance, and therapy, which stands for treatment (Worwood, 2000). For around 6,000 years, numerous prehistoric civilisations such as China, India and Egypt utilised this famous modality under CAM (Krishna et al., 2000; Manniche, 1999). It has proven to be effective for the management of lots of diseases and their complications. A survey of various research studies shows that aromatherapy has attained great attention in the last part of the 20th century and is also getting quite famous in the 21st century because of its significance, growing popularity and extensive usage; it is identified as aroma science healing (Esposito et al., 2014). This therapy utilises essential oils as the principal healing agents, which are supposed to be extremely concentrated materials drawn out or extracted from leaves, flowers, stalks, roots, resins and fruits (Dunning, 2013). There are numerous ways by which these oils can be introduced into a body, for instance, massage, inhalation, natool (therapeutic irrigation) or local applications on the surface of the skin, and seldom are they consumed internally (Ali et al., 2015; Nikhat & Fazil, 2015). Psychoneuroimmunology is all about the association between the functions of the nervous system and immune systems. The study of psychoneuroimmunology aims to apply scientific and clinical knowledge to various neurological diseases, psychological ailments, neoplastic illnesses and immune disorders (Nemeroff, 2013). The specialists in the field of psychoneuroimmunology established that anxiety, stress and depression not only distress the defensive function of the immune system but also alter its balancing function. Socioeconomic status and prolonged diseases, such as asthma, diabetes mellitus, autoimmune disorders, hay fever, urticaria, atopic dermatitis, CVD and hypertension, disturb the mood by giving rise to anxiety, stress

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and depression, all of which adversely affect function and control of the immune system. Cohen published his work 'Behavioral Conditioning of Immunosuppression', in which he suggested a functional relationship between the nervous system and the immune system as the response by the immune system produces cytokines that stimulates the central nervous system (González-Díaz et al., 2017; Marshall, 2011). This excitation of the central nervous system stimulates the HPA axis, which sequentially overpowers the immune reaction through glucocorticoid secretion (Besedovsky & Sorkin, 1977).

Local application and inhalation of essential oils for the management of physical and mental stability are the very fundamentals of aromatherapy. Healing by these oils is acknowledged to alleviate the stress, invigorate and revive the person for the following day's work. The olfactory nerve, i.e. the first cranial nerve beginning from the nose to the brain, is the action's position for these EOs. These oils have well-established antiviral, antimicrobial and antibiotic properties. A range of published manuscripts and research articles in diverse places along with folkloric specialists in the field have proposed them to be beneficial in numerous other ailments like CVD, Alzheimer's disease, carcinoma and commencement of labour pain during pregnancy etc. (Jimbo et al., 2009; Lai et al., 2011; Perry & Perry, 2006; Shiina et al., 2008; Smith et al., 2011). There is an amplified tendency these days to utilise this mode of healing in the management of sleep disorders and cancer (Hwang & Shin, 2015; Lee et al., 2015; Marchand, 2014). For hundreds of years, the EOs have established their significance as a perfume having a healing potential for the mind, body and spirit. These fragrance molecules are precisely potent natural phytochemicals that make the environments free from illness, viruses, microbes and fungus (Baratta et al., 1998). The characteristic multipurpose nature of essential oils, including their antiviral, antibacterial, anti-inflammatory and immunity-boosting abilities, and moreover emotional, hormonal, circulatory, memory-enhancing and relaxing effects is well documented by numerous researchers (Ali et al., 2015; Svoboda & Deans, 1995). The worldwide market for EOs was approximated to be worth 1 billion dollars in 2013 (Williamson, 2014). EOs have been utilised in the beauty and cosmetics world, in domestic goods, in the food and beverage industry for ages, and in recent times they have been in use by pharmaceutical industries. One of the cardiothoracic surgeons from Columbia Medical Center, Dr Mehmet Oz, was among the initial doctors who recognised the potential benefits of aromatherapy. He states that 'Aromatherapy seems to influence the sensitivity of pain' (Oz et al., 1999). Meanwhile, Gattefossé, Maury and Valnet were considered the pioneers of contemporary aromatherapy (Buckle, 2015b).

Historical Uses of Aromatherapy

Ancient Egyptians used aromatic herbs as perfumes (Lawless, 2003), and there are approximately 200 references in the Holy Bible to their usage for spiritual, mental and physical healing (Welsh, 1997). The Ebers papyrus, one of the most eminent ancient medical manuscripts, discussed aromatic plants around 2800 BC. One more manuscript inscribed approximately 800 years later also discusses perfumes and essential oils. These documents were written during the period of construction of the great Egyptian pyramids, which reveals that galbanum, myrtle, eaglewood and frankincense were utilised as a mode of treatment throughout the era of Moses, and

myrrh was used to manage allergic rhinitis. In 1922, when the tomb of Tutankhamun (an ancient Egyptian pharaoh) was opened, 35 perfume jars were located in his chamber tomb, and they were still slightly fragrant. All of the jars were vacant or smashed, and the contents of myrrh and frankincense were thieved (Van Toller & Dodd, 1992). One of the earliest reported uses of fragrant herbs and oils dates back 60,000 years to the discoveries in a funeral place of a skeleton of *Homo sapiens neanderthalensis* that was established to be buried with potent and condensed extracts of grape hyacinth, yarrow, mallow, knapweed and lots of other plants found in the same region that is nowadays Iraq (Erichsen-Brown, 1989). The Chinese technique of making a cloth wet thoroughly in extracts or oils of the aromatic plant (compress) and putting it on the skin specifies how the people of China have appreciated transdermal delivery all this time (something practitioners of allopathic medicine refused for several years). There is a great resemblance between Chinese and Ayurvedic medicine. China was substituting aromatic plants of the Indian subcontinent no sooner than 1000 BC (Swerdlow, 2000). *Charaka* and *Sushruta Samhita*, the earliest Sanskrit medical text of Ayurveda, reported the usage of 700 plants, including fragrant plants, for instance, coriander, ginger, myrrh, sandalwood and cinnamon (Swerdlow, 2000). This ancient Ayurveda text includes explanations for condensation and distillation procedures and essential volatile oils from plants (Rây & Gupta, 1965). Excitingly, customary Indian shamans were recognised as perfumers and were therapists who used aromatic plants' fragrances (Van Toller & Dodd, 1992). Aromatics continues to be a significant fragment of Ayurvedic medicine these days. Theophrastus, who was later known as the father of botany, also described particular uses for aromatic herbs or plants in the era of 300 BC; at that time, physicians who applied aromatic anointing were commonly known as 'latralyptes'. One formulation of aromatics, named kyphi, comprised 16 diverse constituents and was utilised as a disinfectant, an antitoxin for poison, to pacify the skin and also 'make one to sleep calmly, as it alleviated anxiety and enhanced dreams' (Ryman, 1989). Hippocrates, who is famous as the father of medicine, wrote that 'baths from aromatic are beneficial in the management of female diseases, and would so often be suitable for the other ailments too'. Moreover, he was acquainted with the fact that aromatics could have essential antimicrobial properties, and when an outbreak of plague appeared he advised the people to make use of the aromatic plants to keep themselves safe and halt the transmission and advancement of the disease. Hippocrates also states that 'the growth of botanicals manifest an exceptional parallel to the study of medicine' (Hippocrates & Richard Lloyd, 1983). Pedanius Dioscorides, writer of *De Materia Medica* (the basis of western plant medicine) covers nearly 700 plants in his book including fragrant herbs like verbena, basil, rosemary, rose, garlic and cardamom (Holmes, 2007). The work of Galen and Hippocrates was later translated into Arabic and the Arabic physicians were believed to be the most authentic and knowledgeable health experts in the 14th century. One of the famous physicians of the medieval Islamic golden period was Ibn e Sina, known by the name of Avicenna in the western world. He introduced some new fragrant herbs and compounds, for instance, tamarind, senna, camphor, cloves and nutmeg. Moreover, the fragrant water of rose and *Citrus sinensis* flowers was used during that time to make the taste of medicine more pleasant. The doctors of the Arabic world were aware of the effects of several aromatic herbs on human health, such as the sedating effect of inhaling *Hyoscyamus niger* (Swerdlow, 2000). Avicenna is believed to have discovered equipment for distillation of EOs known as the alembic. In the 10th century, numerous traditional

texts were translated from the Arabic language to Latin, and Avicenna's *Al-Qanun fi al-Ṭibb* initially emerged in Europe in the 12th century. There was a belief that foul smells nurture disease, and being encompassed by gratifying fragrances was believed to give defence against illnesses, particularly the plague. Doctors of that time wore costumes to protect themselves from plague and carried plague torches consisting of aromatics to shield themselves (Boeckl, 2000), and moreover sprayed scented waters such as eau de cologne in houses that were affected by infections (Stoddart, 1992). Though the 17th century is recalled as the golden period for phytomedicine, EOs were also extensively utilised in 'mainstream' medicine. Gattefossé (a chemist) learned about aromatherapy accidentally in 1910 when, while working in his research laboratory, he was scalded in an explosion. He sprinted outdoor and rolled on the grass to put an end to the flames. After some days the injuries turned out to be contaminated with gas gangrene; however, one wash from the essential oil of *Lavandula angustifolia* brought an end to the septicity (Buckle, 2015b). Gattefossé devoted his life to investigating essential oils. Lots of his patients were warriors injured in the trenches of the First World War. He made use of essential oils for instance chamomile, thyme, lemon and clove. Till the Second World War, those EOs were applied locally to sterilise wounds and disinfect surgical tools (Ryman, 1991). Henri-Marcel (son of Gattefossé) acquired an interest in essential oils from his father and applied it to the world of pharmaceutical and contemporary medicine development. Valnet, an army doctor, expended considerable time of his life studying and investigating aromatherapy; also he wrote a famous book named *Aromatherapie*, which was the first book about the uses of aromatics and essential oils comprising comprehensive case studies and mentioning frequent references (Buckle, 2015b).

Types of Aromatherapy

The indispensable oils have gained their prominence in cosmetic, healing, medicinal, aromatic and spiritual uses (Evans et al., 2009; Svoboda & Deans, 1995). Some most commonly reported types of aromatherapy are (1) aesthetic aromatherapy, (2) medical aromatherapy, (3) psycho-aromatherapy and (4) olfactory aromatherapy (Figure 6.1).

Psycho-Neuro-Endocrine Immunology

Persistent stress principally signifies the continuous imbalance and instability of the psycho-neuro-endocrine immunological system, and it affects the entire endocrine, psychological and hypothalamus-pituitary axis, which ultimately results in an alteration of cortisol levels. Subsequently, stress promotes tissue inflammation because of the enhancement of the cortisol hormone in the blood. Thus stress indulges body tissues in inflammatory conditions due to the increase in blood cortisol and inflammatory cytokines such as tumour necrosis factor, interleukin-6 and interleukin-1; all of them stimulate the immune system in the sense of pro-inflammation (Bellinger et al., 2008). The interface takes place through all immune cells, particularly the cells of the innate immune system, which are naturally included in the processes of inflammation. Among these immune cells, the mast cells are recognised to be capable of releasing an enormous quantity of histamine and other active materials

Figure 6.1 Types of aromatherapy.

that are responsible for causing dilatation of blood vessels and consequently inflammation. In the past few decades, inflammation has been identified as one of the chief contributing processes in modifications of the lipid profile and in atherosclerosis (Attilio et al., 2018).

The system of psycho-neuro-endocrine immunology discusses how all the sections affect and are affected by the process of inflammation: as a matter of fact, the immune system is also affected by the changes associated with dyslipidemia and depression. A rising number of research studies (Rozanski et al., 1999) is comparing the weight of the hazardous factor associated with negative psychosocial conditions (anxiety, depression, social isolation and hostility) to the traditional biological ones (hypertension, smoking, diabetes, hypercholesterolemia and obesity) within the disease development process in cardiovascular ailments (Halaris, 2013; Rozanski et al., 2005).

Persistent inflammation and stress are the major contributing factors that can also enhance the risk of metastasis and oncogenesis, especially in the lymphatic and glandular systems. The most authentic hypothesis is that an escalation in the synthesis of stress hormones and brain peptides can cause a rise in the levels of cortisol hormone, along with subsequent dysregulation of leptin, insulin and

immune reaction; on the contrary, it also modifies the cell proliferation signalling. Understanding the association between the immune system, neuroendocrine and psychological system, it is not astonishing that a meta-analysis executed on 165 controlled research projects in the field of cancer and its prevention, diagnosis and management determines that psychosocial afflictions are associated with a rise in the frequency and occurrence of carcinoma, a poor prognosis and a rise in death rate (Chida et al., 2008).

Inflammation for a longer duration of time is considered the typical ground for numerous infection-causing processes, and in the earliest period of the 2000s, Franceschi (one of the famous researchers) called 'inflammaging', the amalgamation of chronic low-grade cellular inflammation, the fundamental pattern of senescence and long-standing degenerative processes (Franceschi et al., 2000). The process of inflammation can start and exacerbate because of numerous causes, both of psychological and organic natures, therefore a close connection and interdependence between dysregulation of psycho-neuro-endocrine immunology and inflammaging have been emphasised (Attilio et al., 2018).

Immunomodulatory Activities of Plant's Essential Oils

Essential oils are usually acquired from a variety of fragrant plants; these oils are condensed steam distillates and also consist of manifestations from the rind of citrus fruits. On the basis of their chemistry, essential oils of plants are diversified mixtures; among others, they have the tendency to bind or dissolve with lipids or fats. Their volatile hydrocarbon monoterpenoids include phenols, alcohols, aldehydes, oxides and ketones, while the slightly evaporative sesquiterpenoids include their oxides, alcohols and aldehydes. The influence of smell can be prompt, having an effect on human psychology either directly or indirectly, yet imagining an aroma may have an influence similar to that of the aroma. The combination of various aforementioned constituents in essential oils is responsible for the distinctive smells (Urba, 1996; Walsh, 1996). The essential oils that are breathed in or applied locally on the skin apply quantifiable psychological effects, which indicates that the influence of essential oils is principally pharmacological. This interpretation is reinforced by increasingly described uses of aromatherapy and particular EOs in the treatment of depression, enduring pain, anxiety and a few cognitive diseases, along with stress-associated ailments and insomnia (Heuberger et al., 2001). Aromatherapy is the promptly emerging field amongst other complementary therapies in the United States of America, especially in nurses, and has currently been identified as a permissible and legal part of holistic nursing (Buckle, 2001; Keegan, 2003).

Essential oils of particular plants have immunostimulatory activities applying influence on numerous fragments of the immune system at both molecular and cellular levels, i.e. production of cytokine, antibody and T cells from the immune system (Huang et al., 2008). All parts of plants/herbs, their extracts and herbal products have immunomodulatory properties, for instance, *Glycyrrhiza glabra*, echinacea, *Allium sativum* and cat's claw (Craig, 1999). EOs are extremely distilled and fragrant plant-originated volatile oils with various chemical components that are drawn out by hydro diffusion, steam distillation or pressure. (Manion & Widder, 2017). Aromatherapy is a branch of CAM that introduces essential oils into the body to prevent and manage illnesses by means of numerous methods of administration:

commonly massage, local application or breathing in of fragrant oils (Ali et al., 2015). Several pharmacological activities of essential oils have been investigated and reported; these activities include antioxidant, antibacterial, anticarcinogenic, anti-inflammatory, anxiety alleviating, analgesic, antidiabetic and antidepressant (Bakkali et al., 2008; Bhalla et al., 2013; de Lavor et al., 2018; de Sousa et al., 2015; Edris, 2007; Gandhi et al., 2020; Horváth & Ács, 2015). Clinical validation on the immunomodulatory effects of essential oils is relatively incomplete; however, there seems to be a possibility for certain essential oils to be capable of increasing the number of immune functions. Essential oil of eucalyptus or one of its chief components, cineole, has proven anti-inflammatory activities. The decline in the production of tumour necrosis factor and interleukin-1 and decreased activity of NF-κB were also noticed in monocytes of humans (Sadlon & Lamson, 2010).

It has been observed that the essential oil of *Allium sativum* and a number of its organosulfur compounds enhanced efficient responses in segregated human neutrophils, resulting in enhanced production of ROS and calcium flux (Schepetkin et al., 2019). Essential oil of *Boswellia carterii* revealed a powerful immunomodulatory effect when established on lymphocyte multiplying assay. The peripheral venous lymphocytes were activated by the plant lectin (phytohaemagglutinin) in humans, and the mitogenic response brought about by the existence of frankincense essential oil was similar to that of recognised immunostimulants like levamisole and water-based extract of *Echinacea purpurea* (Mikhaeil et al., 2003). This activation was combined with the manifestation of genes entailed in the production of reactive oxygen species. Correspondingly, the management with essential oil suppressed the most important pro-inflammatory cytokines, interleukin-6 and interleukin-1, putting forth an anti-inflammatory outcome. In one of the studies conducted by Giovannini, the essential oil of *Lavandula* escalated the innate response of the immune system by activating the process of phagocytosis (Giovannini et al., 2016); it also lessened a subsequent inflammatory reaction hence supporting and harmonising the general immune response. *Achillea millefolium* (yarrow) is a fragrant herb utilised in alternative medicine, and its indispensable oil is utilised in aromatherapy (Peterfalvi et al., 2019).

Role of Aromatherapy in Infectious Diseases

With the emergence of new infectious organisms and the reappearance of infectious diseases that have developed resistance to and are now unaffected by conventional antibiotics, possibly communicable diseases will again turn out to be the most usual cause of fatality. Approximately nine million became ill with tuberculosis, whereas 1,400,000 people died from it in the year 2011 (World Health Organization, 2020). MDR TB was found in around 80% of those diseased. Numerous essential oils are proven to be beneficial in vitro (Başer et al., 2009; Crandall et al., 2012; Machan et al., 2006) and in vivo (Sherry et al., 2004) tuberculosis. Some of the essential oils are effective against it (Bueno et al., 2011), and others may increase the efficacy of antibiotics to efficiently combat the infection. Developing resistance against certain antibiotics is hastily getting common for all categories of infectious agents, and aromatherapy aids in fighting against potent and resistant strains of microorganisms. One of the experiments conducted in Germany revealed that an ointment consisting of menthol, pine and eucalyptus essential oils was established to be effective

against infections of the upper respiratory tract in adolescents (Kamin & Kieser, 2007). Numerous patients who came with complaints of bronchitis, catarrh, cold or hoarseness of voice were advised to inhale or rub the ointment locally on the neck area, and the remedy was considered to be tremendous by both patients and physicians (Table 6.1).

Christie Hospital, one of the renowned hospitals in Manchester, UK, also utilises aromatherapy principally for reducing adverse drug reactions in cancer management. The use of essential oil was also mentioned in the research for managing the infection in obese adult women with diabetes and acute leukaemia; those women have damaged skin in the groin area, underneath the abdominal coverings and both breasts. These regions were contaminated with *Pseudomonas*, *Candida*, and methicillin-resistant *Staphylococcus aureus* and slowly released a distinctive obnoxious smell that the patients felt embarrassing. A water-based cream consisting of 3% rosewood, lavender and geranium was locally applied on a regular basis. The quantity of exudate reduced considerably in the first week. The women felt much more contented as the sores got less painful and smelled considerably more pleasant (Buckle, 2015a).

The majority of the general Mediterranean fragrant plants belong to *Rutaceae*, *Verbenaceae*, *Lamiaceae* and *Apiaceae* families (Elshafie & Camele, 2017). In this modern era, it has been proposed that essential oils of plants and their components can be fine alternative larva-killing and pupae-killing agents for the control of mosquitoes (Perumalsamy et al., 2009, 2015). Eugenol and eugenol acetate are the major constituents of clove oil, and it has anticancer, antioxidant, anti-allergic and insect-killing properties (MSN et al., 2016). Fragrant plants hold wide-ranging medicinal and pharmaceutical properties and are consumed as customary medicines in addition to cooking herbs. *Mentha piperita* consists of menthol and demonstrates antiviral and antimicrobial properties (McKay & Blumberg, 2006). Syrian oregano comprises carvacrol and thymol as its active constituents, and these constituents demonstrate antifungal (Soylu et al., 2007) and antibacterial (Alma et al., 2003) properties. Boskabady and Jandaghi researched the effects of carvacrol in *Cavia porcellus* (pigs) and established its bronchodilator outcomes (Boskabady & Jandaghi, 2003). A resting or calming effect on smooth muscles of the trachea was also shown in rabbits and pigs that were exposed to fragrant volatile oil of rosemary (Aqel, 1991). Lu et al. establish that the oil of eucalyptus globules has an anti-inflammatory outcome on constant bronchitis stimulated by LPS in rodents and reduces the hypersecretion of respiratory tract mucins (Lu et al., 2004). In one more study, glycyrrhizin, the constituent of the plant *Glycyrrhiza glabra*, also exhibited antiviral properties when experimented for its antiviral activity in vitro on ten diverse medical strains of SARS coronavirus (Cinatl et al., 2003; Hoever et al., 2005). *Camellia sinensis* also demonstrates strong antiviral properties in severe acute respiratory syndrome coronavirus-2. The antiviral activities of *Camellia sinensis* have also been verified in opposition to the Zika, influenza, HSV type 2, severe acute respiratory syndrome and hepatitis B viruses (Carneiro et al., 2016; Mahmood et al., 2016; Upadhyay et al., 2020) (Table 6.2).

Stress, Anxiety, Depression and Imbalance in Psychoneuroimmunology

Numerous studies have reported the adverse effects of stress on the health of animals as well as humans. In 1975 a research study conducted by Ader and Cohen revealed

Table 6.1 Proven Effects of Aromatherapy in a Few Infectious Diseases

Category of infectious disease	*Aromatherapy used against certain infectious diseases*	*References*
Bacterial infections	Numerous essential oils have antimicrobial properties. For instance, the essential oil of *Coriandrum sativum* proves to be effective against methicillin-resistant *Staphylococcus aureus* and *Streptococcus pyogenes*; further, the minimum inhibitory concentration was established at the quantity of 0.25% and 0.04% correspondingly. Another study evaluated essential oils of lavender, tea tree, patchouli and geranium either in combination or individually against some in vitro strains of methicillin-resistant *Staphylococcus aureus*, among which the blend of tea tree and geranium was found to be most effective against MRSA.	(Casetti et al., 2012; Edwards-Jones et al., 2004)
Fungal infections	In one of the research experiments, the essential oil of *Thymus vulgaris* considerably escalated in vitro destruction of *Candida albicans* by segregated white blood cells in contrast with essential oil-free controls. The oil was found to be similar to fluconazole utilised as a positive control. Another research study experimented with essential oils for assessing their capability to increase the efficacy of fluconazole in opposition to *Aspergillum* species. They established that essential oils consisting of cinnamaldehyde decreased the minimum inhibitory concentration of fluconazole by eight-fold. The same researchers conducted another study, and they established that *Cymbopogon citratus* and *Cymbopogon martini* also had encouraging activity in opposition to *Aspergillum* species. Some more essential oils such as *Lavandula luisieri* and *Juniperus communis* have also been established to be useful against *Aspergillus*.	(Cabral et al., 2012; Tullio et al., 2012; Zuzarte et al., 2012)

(*Continued*)

Table 6.1 (Continued) Proven Effects of Aromatherapy in a Few Infectious Diseases

Category of infectious disease	*Aromatherapy used against certain infectious diseases*	*References*
Viral infections	Star anise essential oil (and all isolated compounds) deactivated free virus particles. Oregano and clove appeared to disrupt the virus envelope. More recently, *Melissa officinalis* was found to be effective against HSV1 and HSV2. Lemon gum (*Eucalyptus citriadora*) and *Eucalyptus globulus* were also found to be effective against the virus. The aforementioned essential oils may be of particular interest to patients with HIV/AIDS as *Eucalyptus globulus* is also found to be effective against MRTB (multiple-drug-resistant tuberculosis) which is common in AIDS patients. Duke wrote that cinnamon (*Cinnamomum verum*) and clove (*Syzygium aromaticum*) had antiviral properties and numerous research studies in the current era show that he was correct.	(Astani et al., 2010; Cermelli et al., 2008; Duke & Bogenschutz-Godwin, 2002; Sadlon & Lamson, 2010; Schnitzler et al., 2001, 2008)
Parasitic infections	In an experiment, *Syzygium cumini* and its essential oil have antileishmanial activities; alpha-pinene, the chief constituent of *Syzygium cumini*, enhanced the lysosomal and phagocytic activities and escalated the production of non-enthused peritoneal macrophages in rodents.	(Rodrigues et al., 2015)
Mosquito-borne diseases	Spearmint's essential oil has demonstrated a considerable effect against primary third-stage larvae of three kinds of mosquito: *Aedes aegypti*, *Culex quinquefasciatus* and *Anopheles stephensi*. Furthermore, essential oils from *Zingiberaceae* and *Apiaceae* plant families have been accounted to have strong repellent, larva-killing, pupae-killing and adulticidal activities against *Culex quinquefasciatus*, *Ae. aegypti*, *Culex pipiens* and *Anopheles stephensi*. Likewise, the neem plant extracts, leaves of *Vitex negundo*, *Alpinia galangal* and *Tribulus terrestris* have also been researched as potential mosquito repellents. Research also established that celery, dill seed, turmeric, caraway, cumin seeds, fennel, *Melia azedarach*, *Petroselinum crispum*, *Piper nigrum* and their essential oils enhanced conventional mosquitocidal activity against all species of mosquitoes.	(Govindarajan et al., 2013; Phukerd & Soonwera, 2013; Shaalan et al., 2005; Sihoglu Tepe & Tepe, 2015)

Table 6.2 General Description of Essential Oil of Common Plants and Their Functions

Biological activity	*Essential oil of medicinal plant*	*Part used to extract oil*	*Description of function*	*References*
Antimicrobial activity	*Achillea ligustica*	Aerial parts	Inhibits *Streptococcus mutans*	(Ahmadi et al., 2011)
	Allium sativum	Bulb	Inhibits *Enteriobacteriacae*	(Hussein et al., 2017)
	Artemisia longifolia	Aerial parts	Inhibits *E. coli, S. aureus, S. epidermidis*	(Lopes-Lutz et al., 2008; Rashid et al., 2013)
	Cinnamomum zeylancium	Bark, leaves	Works against *Enterobacteriaceae, S. aureus, Streptococcus pyogenes, S. pneumonia, Enterococcus faecalis, E. faecium, Bacillus cereus, Acinetobacter lwoffii, Enterobacter aerogenes, E. coli, Klebsiella pneumonia, Proteus mirabilis, P. aeruginosa, Salmonella typhimurium, Clostridium perfringens, Mycobacterium smegmatis*	(Mota et al., 2019)
	Coriandrum sativum	Leaves	Works against *S. aureus, Bacillus* spp., *E. coli, Salmonella typhi, K. pneumonia, Proteus mirabilis, P. aeruginosa*	(Silva et al., 2011)
	Foeniculum vulgare	Leaves	Shows inhibitory effects against *S. typhimurium, E. coli*	(Ilić et al., 2019)
	Mentha piperita	Aerial part	Shows inhibitory effects against *S. aureus, S. typhimurium, V. parahaemolyticus*	(Ahmad et al., 2014)
	Nigella sativa	Seeds	Show inhibitory effects against *S. aureus, B. cereus, E. coli, P. aeruginosa*	(Kazemi, 2014)
	Ocimum basilicum	Leaves	Works against *Brochothrix thermosphacta, E. coli, L. innocua, L. monocytogenes, P. putida, S. typhimurium, S. putrefaciens, M. flavus*	(Stanojevic et al., 2017)

(*Continued*)

Table 6.2 (Continued) General Description of Essential Oil of Common Plants and Their Functions

Biological activity	*Essential oil of medicinal plant*	*Part used to extract oil*	*Description of function*	*References*
	Pimpinella anisum	Seed	Inhibits *S. typhimurium*, *E. coli*	(Abdel-Reheem & Oraby, 2015)
	Piper nigrum	Seeds	Decreases *S. aureus* and *E. coli*	(Morsy & Abd El-Salam, 2017)
	Rosmarinus officinalis	Flower	Inhibits *E. coli*, *S. typhimurium*, *B. cereus*, *Bacillus subtilis*, *S. aureus*, *S. agalactiae*, *S. epidermidis*, *S. aureus*, *P. vulgaris*, *P. aeruginosa*, *K. pneumonia*, *E. faecalis*, *B. thermosphacta*, *L. innocua*, *L. monocytogenes*, *P. putida*, *S. typhimurium*, *S. putrefaciens*, *M. smegmatis*	(Mekonnen et al., 2016)
	Salvia officinalis	Aerial part	Found to be beneficial against *S. aureus*, *P. stuartii*, *E. coli*, *Shigella sonnei*, *Sarcina lutea*, *M. flavus*, *B. thermosphacta*, *E. coli*, *L. innocua*, *L. monocytogenes*	(Damjanovic-Vratnica et al., 2008)
	Syzygium aromaticum	Leaves, flower bud	Works against *P. aeruginosa*, *Enterobacteriaceae*	(Radünz et al., 2019)
	Thymus vulgaris	Aerial part	Shows inhibitory effects against *L. monocytogenes*, *E. coli*, *S. typhimurium*, *S. aureus*, *C. botulinum*, *C. perfringens*, *S. sonnei*, *S. lutea*, *M. flavus*, *B. thermosphacta*, *L. innocua*, *L. monocytogenes*, *P. putida*, *S. putrefaciens*	(Borugă et al., 2014)
Antifungal activity	*Aegle marmelos*	Leaves	Diminishes *Candida albicans*, *Aspergillus niger*, *Fusarium oxysporum*	(Balakumar et al., 2011)
	Cinnamomum zeylancium	Bark, leaves	Inhibits *C. albicans*, *C. parapsilosis*, *C. krusei*	(Trajano et al., 2012)
	Coriandrum sativum	Leaves	Works against *C. albicans*	(Freires et al., 2014)

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Table 6.2 (Continued) General Description of Essential Oil of Common Plants and Their Functions

Biological activity	*Essential oil of medicinal plant*	*Part used to extract oil*	*Description of function*	*References*
	Feoniculum vulgare	Seeds	Inhibits *Alternaria alternata*, *F. oxysporum*, *A. flavus*	(Garzoli et al., 2018)
	Melaleuca alternifolia	Aerial part	The plant is proven to be beneficial against *Alternaria* spp., *A. flavus*, *A. fumigates*, *A. niger*, *Blastoschizomyces capitatus*, *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, *Cladosporium* spp., *C. neoformans*, *Epidermophyton floccosum*, *Fusarium* spp., *Malassezia furfur*, *Microsporum canis*, *M. sympodialis*, *M. gypseum*, *Penicillium* spp., *Rhodotorula rubra*, *Saccharomyces cerevisiae*, *Trichophyton mentagrophytes*, *T. rubrum*, *T. tonsurans*, *Trichosporon* spp.	(Terzi et al., 2007)
	Myrtus communis	Leaves	Inhibits *C. albicans* and *A. flavus*	(Bouzabata et al., 2013)
	Nigella sativa	Seeds	The oil is beneficial against *A. flavus*, *Fusarium moniliforme*, *F. graminearum*, *P. viridicatum*	(Mahmoudvand et al., 2014)
	Ocimum species	Leaves, flowers	*C. albicans*, *C. tropicalis*, *C. glabrata*, *P. notatum*, *R. stolonifer*, *M. mucedo*, *A. ochraceus*, *A. versicolor*, *A. niger*, *A. fumigates*, *T. viride*, *P. funiculosum*	(Vieira et al., 2014)
	Rosmarinus officinalis	Leaves	Oil of *Rosmarinus* is found to be useful against *C. albicans*, *M. gypseum*, *M. canis*, *A. cajetani*, *T. violaceum*, *T. mentagrophytes*, *E. floccosum*, *T. rubrum*, *T. tonsurans*, phytopathogens *B. cinerea*, *P. oryzae*	(Özcan & Chalchat, 2008)

(*Continued*)

Table 6.2 (Continued) General Description of Essential Oil of Common Plants and Their Functions

Biological activity	*Essential oil of medicinal plant*	*Part used to extract oil*	*Description of function*	*References*
	Syzygium aromaticum	Leaves	Inhibits *A. fumigatus*, *C. albicans* and *Candida* spp.	(Aguilar-González et al., 2015)
Antiviral activity	*Achillea fragrantissima*	Aerial parts	Beneficial against ORF virus (a parapox virus)	(S G Zeedan, 2014)
	Artemisia arborescens	Aerial parts	Decreases herpes simplex virus type 1 (HSV-1)	(Saddi et al., 2007)
	Hyssopus officinalis	Flower and leaves	Diminishes HSV-2, HIV	(Fatemeh Fathiazad, 2011; Hristova et al., 2015)
	Lepechinia salviifolia	Leaves	Inhibits HSV-1 and influenza virus	(Wani et al., 2021)
	Matricaria chamomilla	Flower	Found to be beneficial against HSV-2	(Satyal et al., 2015)
	Melissa officinalis	Leaves	Inhibits HSV-2 and influenza A virus	(Pourghanbari et al., 2016)
	Santalum album	Wood	Diminishes HSV-1 and HSV-2	(Benencia & Courrèges, 1999)
	Syzygium aromaticum	Flower	Oil of clove is beneficial against HSV-1	(Cortés-Rojas et al., 2014)
	Terminalia chebula	Fruit	Diminishes HSV-1	(Benencia & Courrèges, 1999)
	Thymus vulgaris	Flower and leaves	Inhibits HSV-2 and coronavirus	(Catella et al., 2021)
	Trachyspermum ammi	Leaves	Useful against Japanese encephalitis virus (JEV)	(Roy et al., 2015)
	Zingiber officinale	Root	Demonstrates inhibitory effects against HSV-2, adenovirus and polivirus	(Mbadiko et al., 2020)

the consequences of stress on the immune system. Neuroimmunophysiologists have established that anxiety, stress and depression not only disturb the defensive function of the immune system besides it change its controlling function (González-Díaz et al., 2017). Stress modifies the immune reaction by means of the psycho-neuro-immuno-endocrine pathway and the HPA axis (Marshall, 2004) and through the release of norepinephrine, cortisol, epinephrine and interferon-gamma by T lymphocytes. Raised levels of pro-inflammatory cytokines, for instance, IFN-γ and a prompt but tissue-deteriorating cellular immune reaction, constitute the response of the immune system (Buske-Kirschbaum et al., 2006). Currently, it has been established that epigenetic causes also stimulate the progression of inadequate stress reactions, paving the route for a persistent stress response instead of an acute stress response (González-Díaz et al., 2017).

The imbalances in the neuro-immunological system have been recognised as significant aspects and likely biomarkers for psychiatric ailments such as depression, schizophrenia and anxiety disorders (Peters et al., 2017). Psychosocial stress because of any reason, for instance, insecurity of a job, has been related to imbalances in production and secretions of neurotransmitters leading to anxiety, disturbances in sleep and adrenal fatigue (Head & Kelly, 2009). These changes may lead to several health-related problems counting gastrointestinal disturbances, headache, weakening of the immune system and cardiac diseases (Hou et al., 2017); furthermore, the imbalances in the neuroimmunological pathways may lead to cognitive dysfunctions, depression and inflammation in the neurological system, whereas the social stress may lead to an imbalance in the autonomic nervous system's supply towards the heart and may disturb the heart rate. The decreased heart rate may be seen in patients with numerous anxiety diseases, including posttraumatic stress disorder. The possible biomarkers, for instance, neuropeptide Y, CRF (corticotropin-releasing factor) and cytokines (i.e. IL-6), may specify the comorbidity between autonomic disparity and stress-related mental ailments (Wood, 2014). While at the systemic stages, causes such as obesity and psychosocial stress, particularly a leaky gastrointestinal tract, may result in the disproportion among pro-inflammatory T lymphocytes and regulatory cells (Haroon et al., 2012).

Psychoneurological and Sleep-Inducing Effects of Aromatherapy

Nearly 30% of the common population is suffering from lack of sleep or insomnia (Jahangir et al., 2008). It is assessed that 40% of all patients with insomnia have a parallel psychiatric disorder (Ancoli-Israel, 2006). Depression and insomnia have a mutual course of pathology. Arroll et al. (2012) established 50% of insomniac research participants had depression. Sleep disorders affect physical and cognitive functioning, and insomniacs are more susceptible to accidents (Arroll et al., 2012). Insomnia disturbs performance at the job and results in time off. Moreover, it affects QOL. Females are 1.4 times more prone to have insomnia as compared to males, whereas old-aged women are greatly at risk (Jahangir et al., 2008). In accordance with the American Sleep Association (ASA), continual struggle in falling asleep, remaining asleep or being deprived of the quality of sleep for no less than one month is recognised as insomnia. Approximately 30 years back, the caption 'Lavender Beats Benzodiazepines' presented the concept that aromatherapy could be beneficial for

insomnia. Moreover, the researcher defined the utilisation of essential oils of geranium, cardamom, lavender, mandarin and marjoram as helping aids to sleep in a hospital. The therapy can be useful to make the patients less anxious and tense, hence allowing them to sleep or bring back a regular pattern of sleep. *Lavandula angustifolia* has an extensive account of usage in aromatherapy to encourage relaxation, sleep and decrease anxiety (Buckle, 2015b). In 1973, Atanassova-Shopova and Roussinov established that terpineol and linalool were the active constituents of *Lavandula angustifolia*, and they had a discouraging effect on the CNS (Atanassova-Shopova & Roussinov, 1970). Oral dosages of linalool were established to have sleep-inducing and anti-epileptic effects in rats in research conducted by Elisabetsky et al. (Elisabetsky et al., 1995). One of the studies conducted by a Japanese (Yamada et al., 1994), agreed that anticonvulsant activities were established in rodents after inhaling lavender. Linalool, one of the chief constituents of lavender, was identified to encourage sleep in rats (Linck et al., 2009). Buchbauer et al. (1991) found out in Germany that lavender had a tranquillising effect when breathed in by rodents. Excitingly, the more restless the animal was, the more powerful the tranquilising effect of the lavender. Lavender was also reported to have anti-stress activities. One of the studies also mentioned that inhalation of lavender amplified the proportion of deep-wave sleep in 31 men and women in a sleep laboratory (Goel et al., 2005). Goel also explains aromatherapy as a 'non-experimental process for transforming mood and sleep'. Jager et al. established that *Citrus aurantium* or neroli had a calming effect on rodents. Moreover, neroli revealed quantifiable anti-anxiety effects and is frequently recommended for treating anxiety (Jäger et al., 1992). Essential oils of *Tilia cordata* and *Passiflora incarnate* also have sedative and calming effects (Buchbauer et al., 1992). A current analysis of herbal blends utilised for depression, apprehension and insomnia in individuals established thorough studies conducted upon humans and it specified that passionflower had a quantifiable anti-anxiety effect; still, further research studies are needed (Sarris & Byrne, 2011). Passionflower emerges to function by moderating the gamma-aminobutyric acid system (Appel et al., 2011). One of the research establishes that the essential oil of *Nigella sativa* had a relaxing effect more potent than the medicine chlorpromazine and also acted as a painkilling agent. The research proposed that the black seed is comprised of an opioid-like constituent (Buckle, 2015b). Currently, further research projects on animals have focused more on the anticonvulsant (Hosseinzadeh & Parvardeh, 2004) and anti-anxiety effects of aromatherapy (Gilhotra & Dhingra, 2011) in rats. It was discovered that the essential oil of rose has calming and tranquilising effects. Subsequent research by Hongratanaworakit (2009) rediscovered the sedative effects of rose oil; moreover, rose oil has the potential to decrease respiratory rate and SBP, which ultimately leads to the reduction in autonomic stimulation. The distilled petals of rose had the maximum effect on insomnia, with around 66.6% asserting complete alleviation of insomnia (Hongratanaworakit, 2009). Another study conducted by Komori et al. (2006) discovered the influence of inhaled EOs blend on 29 patients with primary insomnia, which were totally dependent upon benzodiazepines. The blend consisted of 6% orris, 8% rose, 12% juniper and 35% sandalwood oil. The outcomes of the research revealed that 26 research participants were capable of minimising their drug dosage while 12 participants were able to get themselves completely detached from the sleeping pill (Komori et al., 2006). Seong et al. (2013) utilised a blend of *Origanum majoranum*, *Cananga odorata*, *Lavandula angustifolia* and *Citrus aurantium* and the outcomes of two weeks of RCT revealed a noteworthy drop in pulse rate

and BP (Buckle, 2015b). Aromatherapy can be a great option for the management of psychiatric disorders and it is free from unwanted or negative effects that are usually related to contemporary medicines. The most frequently utilised EOs for dementia therapy in RCTs have been *Melissa officinalis* and *Lavandula angustifolia* individually or in the form of a blend. The health benefits consist of decreases in sleep disorders, anxiety, wandering, challenging behaviour and withdrawal from social life. Lots of essential oils are related to mood enhancement suggestive of possible application for the management of depression (Perry & Perry, 2006).

SARS-CoV-2 and Aromatherapy

The botanicals that have medicinal properties may help in the prevention and management of SARS-CoV-2, especially in the communities that are more susceptible to catching the infections, based on previous research and demonstration of protection against severe acute respiratory syndrome in humans throughout the outburst of SARS. It was suggested that a blend of conventional and herbal medicines did not reduce the death rate, however, it was determined that it may enhance the quality of life, decrease the chances of pulmonary infiltration and also decrease the requirement and dosage of medications such as steroids (Liu et al., 2012). Comprehensively, 640 participants with severe acute respiratory syndrome took part in the experiment, which comprised 12 Chinese herbal medicines. In accordance with the recent study (Vellingiri et al., 2020), natural medicines like herbs, and their essential oils, may have a role to play in order to reduce the potency and strength of COVID-19 and neutralise its effects. Numerous research studies revealed that there is a resemblance between SARS-CoV-2 and MERS, SARS, influenza and cold viral infections. So the herbal medicines and their essential oils may provide protection against the SARS-CoV-2 virus and may be given as a remedy directly focusing on the disease.

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Chapter 7

Stress Management and Meditation

Introduction

Mental or psychological stress is a global health epidemic associated with over 23 million deaths annually all around the globe (Fink, 2016; Go et al., 2004). Stress is an actual threat to health, which can transiently trigger irritability, muscle tension, headaches, emotional uncertainty (Hassmén et al., 2000), increased blood pressure and heart rate (Schneiderman et al., 2005). Furthermore, for a prolonged duration, stress may promote the commencement of depression, anxiety (Netterstrom et al., 2008), exhaustion, severe fatigue (Leone et al., 2011), chronic disorders (Wolever et al., 2012) and cognitive conditions like executive function problems (McEwen & Sapolsky, 1995). More precisely, stress may give rise to the persistent adaptation of the immune system and the neuroendocrine system (McEwen, 2003). Persistent stress is related to cognitive deterioration of the hippocampal areas of the brain that control learning and memory (Hains et al., 2009; van der Kooij et al., 2014), and moreover, to adverse physiological outcomes including decreased immunity and enhanced inflammation (Marsland et al., 2017).

The beginning of the notion of stress can be tracked down to the fifth century BC to Empedocles; though, in the latter part of the 1930s, Hans Selye was the first person to utilise the word stress almost as it is utilised nowadays (Chrousos et al., 1988; Mason, 1975). The factors that modify equilibrium, or homeostasis (regular modulatory rhythms), are named stressors and consist of a range of physiologic, environmental and psychological stimuli. A multitude of studies have shown that a range of mental stressors, e.g. loss of self-esteem, bereavement and academic pressure, can result in laboratory verification of immunologic deterioration; the anatomic constitution inside the nervous system and pathways of the neuroendocrine system included in the arbitration of these effects have been explained further (Peterson et al., 1991).

The immune system, central nervous system and endocrine system are compound systems associated with each other. The stressful events of life and negative

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emotions they produce can abnormally regulate the immune reaction by affecting the sensitive interactions amid these systems (Glaser & Kiecolt-Glaser, 2005). The field of psychoneuroimmunology deals with the study related to the associations of psychological factors with the immune system and neuroendocrine system; moreover, the outcomes for human behaviour and higher brain function (Dantzer, 2010). The principal focus of psychoneuroimmunology has been to comprehend the association between inflammatory reactions and stress.

Though intense inflammation is an adaptive reaction to infection or any physical injury, prolonged and/or exaggerated inflammatory reactions are injurious to health (Dhabhar, 2014). Persistent inflammation caused by prolonged stress has been ultimately associated with risk for several disorders, including diabetes, infectious diseases, autoimmune disorders, particular cancers and cardiovascular disorders, as well as general weakness and fatality (Dhabhar, 2014; Glaser & Kiecolt-Glaser, 2005; Padro & Sanders, 2014; Webster Marketon & Glaser, 2008). One possible description of the mechanism associating inflammation and chronic stress in the commencement of a broad range of ailments is that long-standing stressors ensue in resistance of glucocorticoid receptors, which consequently causes dysfunctioning of the hypothalamus-pituitary-adrenal axis and unnecessarily intervenes with the appropriate control of inflammation (Cohen et al., 2012).

As an adaptive reaction to stress, there is a modification in the levels of different hormones in the blood, including catecholamines, corticotropin-releasing hormones, thyroid hormones and cortisol. These alterations may be needed for the fight-or-flight response of the person to stress. However, prolonged stress exposure may lead to numerous detrimental outcomes leading to several endocrine ailments. Moreover, stress leads to modification in several endocrine diseases' clinical status or course (Ranabir & Reetu, 2011). The connection between the commencement of Graves' disease and stressful life events was primarily reported in 1825 by Parry. The previous data reveals a great incidence of thyrotoxicosis among Nazi prison camp refugees. Mental stress has been documented in up to 65% of youthful patients with physical stress and hyperthyroidism in several elderly patients (Hoffenberg, 1974).

Graves' disease patients not only had a considerably significant amount of stressful events in life, but they also had a huge impact of stressful and negative life events contrasted with normal controls and patients with toxic nodules (Matos-Santos et al., 2001). One of the studies documented a substantial rise in Graves' disease incidence throughout the civil war in Eastern Serbia (Paunkovic et al., 1998). Stress may give rise to a weakness in immunological surveillance, ultimately causing the synthesis of thyroid-stimulating hormone receptor antibodies (Ranabir & Reetu, 2011). Moreover, stress can lead to menstrual abnormalities, anovulation and amenorrhea in females. Amid newly imprisoned females, along with stress, 33% had irregularities of menstruation and 9% had amenorrhea (Allsworth et al., 2007), and in males, there can be changed morphology and motility of sperm and diminished sperm count (McGrady, 1984). Oligospermia, impotency and ejaculatory problems may be related to psychological components in males' infertility (Palti, 1969). Psychological stress may give rise to persistent stimulation of the neuroendocrine systems. Stress hormone (cortisol) promotes central obesity, a rise in ghrelin and a leptin drop, and encourages enhanced appetite and food consumption. This condition gives rise to the recent obesity epidemic (Siervo et al., 2009).

Thus, it has been suggested that persistent stress causes a reduction in the functioning of the immune system related to increased vulnerability to contagious

or infectious ailments (De Andrés-García et al., 2012; Dhabhar, 2014), while acute stress may stimulate the immune system as an adaptive reaction (Paszynska et al., 2016). Earlier investigations reveal that aerobic exercise and MBIs (mindfulness-based interventions) could make mental health better (Eisendrath et al., 2016; Lavie et al., 2016; Rebar et al., 2015), giving complementary and practicable options for medical management (Dubbert, 1992; Kabat-Zinn, 1982; Martin & Dubbert, 1982). A variety of mindfulness-based methods has been invented to increase quality of life and decrease stress (Bohlmeijer et al., 2010; Shapiro, 2009). Particularly, there is a rising research interest in the influence of meditation on overall health benefits (Davidson et al., 2003; Jacobs et al., 2011). Meditation is believed to be a complex and conscious process of cognition, including receptive awareness and concentration (Tang et al., 2015). Instances of meditation include qigong, transcendental meditation, mindfulness-based intervention and spiritual meditation (Ospina et al., 2007). This chapter will discuss the detrimental effects of stress, how stress affects hormonal secretions, what meditation is and what its types are, what the effects of meditation are on inflammatory markers and EEG of the brain, how deep breathing and meditation help in reducing blood pressure and how meditation stimulates the immune system and capability of the body to heal (Figure 7.1).

The Association between Stress and the Immune System

The downregulation and upregulation in functions of the immune system may be observed as an adaptive response modulated by stress hormones. The persistent secretion of stress hormones can initiate a kind of physiological 'wear and tear' (allostatic load), giving rise to dysfunctioning and suppression of the immune system (McEwen, 1998; Zachariae, 2009). Thus, persistent stress weakens or damages the immune system reaction (Segerstrom & Miller, 2004) as well as precipitates inflammation (Pace et al., 2009; Weik et al., 2008). Precisely, raised CRH (corticotrophin-releasing hormone) stimulates the synthesis of proinflammatory cytokines (Wang et al., 2003), which provoke inflammation as a primary defence against infection or injury. These proinflammatory cytokines comprise interleukin 8 (IL-8), TNF-α, interleukin 1 (IL-1) and interleukin 6 (IL-6) (Glaser et al., 1999). Moreover, an acute inflammatory protein, i.e. C-reactive protein, functions as an indicator of inflammation and because of the escalated levels of CRP inflammation taking place (Sproston & Ashworth, 2018). Particularly, IL-6 (interleukin 6) enhances the synthesis of C-reactive protein (Tanaka & Kishimoto, 2014). Another complex protein, NFκB, is accountable for intervening in the production of proinflammatory cytokines while it plays a part in inflammation (Lawrence, 2009). Similar to C-reactive protein, the activity of NFκB is escalated with inflammation. The persistent increase in activity of NFκB is related to inflammatory disorders such as atherosclerosis, inflammatory bowel disease (IBD) and arthritis.

Though persistent elevation of proinflammatory cytokines impedes the ability of the body to combat infections and manage wounds as well as enhances individuals' risk for disorders such as osteoporosis, cardiovascular diseases and type 2 diabetes mellitus (Chrousos, 2000), increased C-reactive protein and interleukin-6 are related with an enhanced risk of cardiovascular disorder and fatality (Sproston & Ashworth, 2018). Psychological stress is identified to increase both C-reactive protein and IL-6 (interleukin 6) (Kiecolt-Glaser et al., 2003; Steptoe et al., 2007), hence

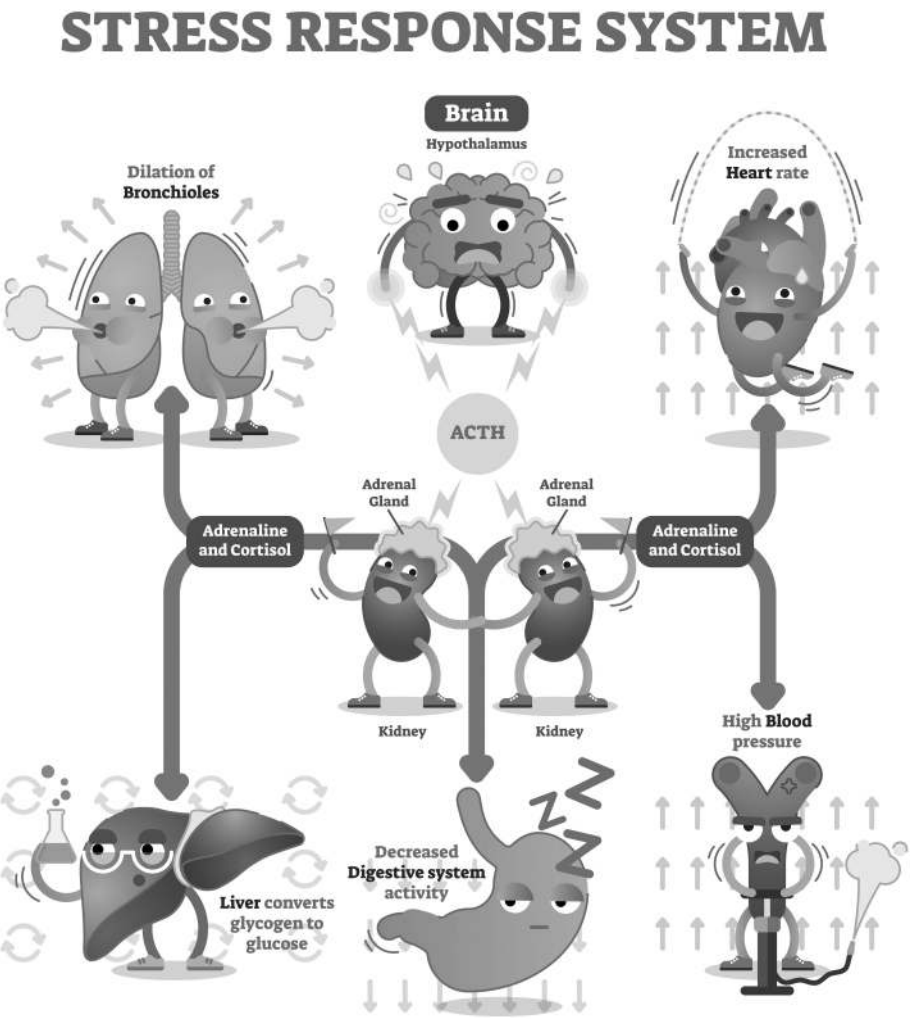

Figure 7.1 Stress response system.

synthesising enhanced levels of proinflammatory cytokines in circulation (Creswell et al., 2016; DeRijk et al., 1997; Zhou et al., 1993), decreasing the response of the immune system towards injury and infection (Glaser et al., 1999). Negative emotions can also subdue the functions of the immune system by means of their propensity to stimulate the shortening of telomeres and enhanced activity of NFκB (Epel et al., 2009; O'Donovan et al., 2012; Steptoe et al., 2007; Zachariae et al., 1991).

Numerous people have experienced the association between getting sick and stress. Herpes, colds, allergies and influenza appear to be worse when an individual is extremely stressed at home or in the workplace. Due to intrinsic associations identical to these, numerous researchers today are experimenting with whether (and how) diseases and stress are associated. Research studies focused on discovering the association between the immune system and stress have explored the impact of factors such as divorce, bereavement, mental arithmetic, examinations,

unemployment and taking care of a relative suffering from Alzheimer's disease. Generally, these studies discover that stress is associated with modifications in both the number of immunoglobulins in blood and the quantity of WBCs in circulation.

Furthermore, stress is related to alterations in the performance of immune cells (Herbert, 1994). There are now convincing verifications that stress reactions can give rise to clinically pertinent immunosuppression (Kiecolt-Glaser et al., 1996; Vedhara et al., 1999) as well as other forms of dysfunction in the immune system (Farber & Nall, 1993; Jacobs et al., 2011; Lechin et al., 1994; Leker et al., 1998; Vasquez et al., 1992). In situations in which the stressor can't be lessened quickly, it would be useful to impede the actions or synthesis of those mediators of stress that are principally accountable for unfavourable immunological reactions (Pruett, 2003).

How Stress Affects the Hormonal Secretions

The levels of different hormones alter in reaction to stress. Responses to stress are related to increased secretion of many hormones, including prolactin, catecholamines, glucocorticoids and growth hormones, the outcome of which is to enhance the energy sources' mobilisation and modify the person to their new situation. The pituitary-adrenal axis activation is a renowned reaction of the neuroendocrine system to stress, encouraging endurance. Activation of the pituitary-adrenal axis results in CRF (corticotrophin-releasing factor) secretion from the hypothalamus. Subsequently, corticotropin-releasing factors encourage the pituitary to release adrenocorticotrophin hormone, 3-endorphin and 8-lipotropin. Levels of these hormones in the blood can enhance two to five times in humans during stress (Hargreaves, 1990).

Activation of the pituitary-adrenal axis is related to the secretion of catecholamines. This gives rise to enhanced retention of Na+, enhanced cardiac output, blood flow to skeletal muscles, decreased motility of intestines, dilatation of bronchioles, cutaneous vasoconstriction, enhanced glucose and behavioural stimulation (Goldstein, 1987).

In women, regular menstrual cycles are also disrupted because of the suppression of circulating hormones from gonads and gonadotropins in stressful conditions (Cameron, 1997); continued stress exposure can lead to total disablement of functions of the reproductive tract (Lachelin & Yen, 1978). Generally, the functions of the thyroid gland are downregulated throughout stressful conditions, while the levels of T3 and T4 are reduced with stress. Additionally, stress decreases the secretion of TSH (thyroid-stimulating hormone) by means of glucocorticoid activity in the CNS (central nervous system) (Helmreich et al., 2005). Reduction of insulin along with a rise in its antagonistic hormones during stress can give rise to hyperglycemia (stress-induced) (Halter et al., 1984).

Meditation as a Relaxation Technique

Despite expeditious progress in health care in recent times, other traditional types of therapies have acquired admiration since numerous people, discontented with contemporary medicinal approaches, have been enticed to alternative treatments.

One of the reasons for this change may be the rise in the median age of the people and the intensified awareness of chronic disorders and fatalities associated with the lifestyles of individuals (Coulter & Willis, 2004).

Numerous centuries ago, meditation initially appeared in Eastern civilisations as an essential fragment of both Buddhist and Hindu religions. However, the precise duration of its origin is not known; the earliest written meditation references have existed since the era of the earliest Vedas—a compendium of Hindu sacred writings—while by 500 BC, novel types of meditation started to develop in Taoist China and Buddhist India. Particularly, Buddhism prompted the expansion of meditation all around the Asian regions, and the Silk Road development speeded up its transferral towards the west, initiating about the first century AD (Elverskog, 2010) (Figure 7.2).

However, attraction to Eastern types of meditation did not thoroughly flourish in America till the post-war era. In the 1960s, the hippie movement appeared as an opposition to the Vietnam War. Eventually, this subcultural (hippie) movement grew exasperated with the materialism of Americans, the usual cultural standards of the middle class and social commitment to traditional ideas and values with

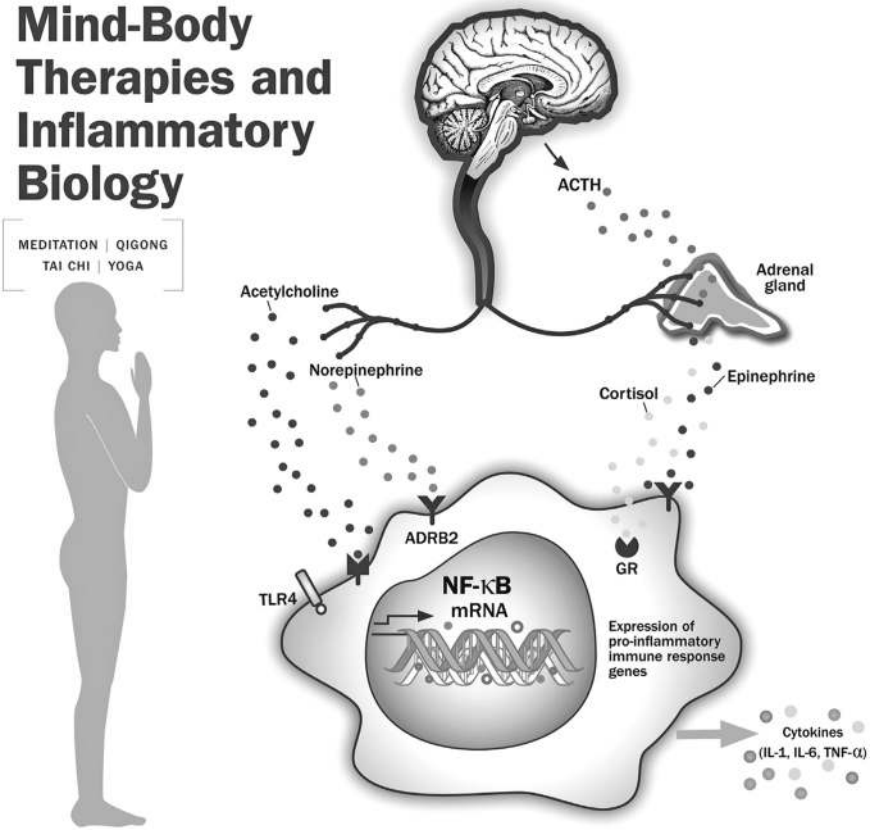

Figure 7.2 Potential pathways linking mind-body therapies and inflammatory biology, focusing on neuroendocrine mechanisms. (Source: illustration acquired from 'Mind–Body Therapies and Control of Inflammatory Biology: A Descriptive Review' (2015) by J. E. Bower and M. R. Irwin, *Brain, Behavior, and Immunity*.)

Figure 7.3 Meditation in sitting position.

resistance to innovation or change. As a segment of this 'revolter uprising', hippies adopted the spiritual practices of Eastern regions and psychoactive medicines to acquire 'greater' consciousness levels (Coleman, 2002). With its commencement in the western regions, various studies describe promising benefits of meditation on health. Most significant among these primary studies was the experimentation of Jon Kabat-zin (Thibodeaux and Rossano, 2018), who integrated the practice of sitting meditation along with body scan and yoga in his MBSR eight-week programme, which teaches complete attentiveness in day-to-day practice. Kabat-Zinn (Black et al., 2014) explained mindfulness as 'rendering attention on objectives, in the present situation and non-judgmentally, to the unravelling of experience very quickly as time passes'. Scientific verifications from research studies and meta-analyses have demonstrated the outcomes on the benefit levels of MBI (mindfulness-based interventions), among other things on depression (MacKenzie et al., 2018), stress and state of being healthy and happy (Goyal et al., 2014), physical pain (Hilton et al., 2017), sleep (Rash et al., 2019), anxiety and inflammatory reactions (Hoge et al., 2018). Moreover, approaches such as mindfulness training for the examination in the selfish–selfless range are getting into mainstream clinical care for treating stress and pain. It is essential to identify that at least three different kinds of meditation have been established to have significant implications on health, i.e. qigong, TM and mindfulness meditation (Thibodeaux & Rossano, 2018) (Figure 7.3).

Types of Meditation

Mindfulness and Associated Interventions

The word 'mindfulness' is frequently associated with Buddhism since it is nowadays being used to surpass its cultural and spiritual roots. In western medicine, as a practice, mindfulness has been applied to mitigate existing diseases in an attempt

to inhibit any pathology (Carlson et al., 2004; Hofmann et al., 2010; Kabat-Zinn, 2013). The term mindfulness is a translation of long-established Eastern expressions such as '*dranpa*' in the Tibetan language, '*smrti*' in Sanskrit and '*sati*' in the Pali language. Meanwhile, in modern psychology, mindfulness is contemplated to be the consciousness one acquires by deliberately taking part in an accepting and discriminating manner in the individual's present moment-to-moment experience (Kabat-Zinn, 2003; Shapiro & Carlson, 2009). Mindfulness is frequently mentioned as a practice of consciousness, cultivation and teachings of perception and presence. Though related to meditation, mindfulness goes beyond a technique of meditation or practice. Mindfulness can be a situation or an instant experience of being existent (Jazaieri & Shapiro, 2017).

Mindfulness is acquired when the person evolves an unconcerned awareness of their feelings, body, mind states and sensations. Mindfulness is not considered to be the same as subduing thoughts. In lieu of that, a person who has achieved mindfulness has an uncomplicated awareness of sensations, thoughts and feelings. Consequently, elapsing feelings or thoughts are recognised but in a non-judgmental and disconnected manner. Thus, the person is capable of freeing their consciousness and completely experiencing all attributes of life, overcoming negative thoughts and feelings in a healthy manner (Thibodeaux & Rossano, 2018).

Successively, the state of mindfulness can transform into more of a disposition or characteristic over time, basically an elemental manner of being. Contemporary experimental data back up this notion that enhancing the state of mindfulness over recurrent meditation sessions may eventually give rise to one having a greater mindful trait or disposition (Kiken et al., 2015). Researchers have experimentally and theoretically associated mindfulness with ameliorated physiological health in various areas (Siegel, 2007). Data from a recent study has revealed that the practice of meditation, i.e. mindfulness, can have an impact on the functions and configuration of the brain (Hölzel et al., 2010).

Initial proof has also revealed modifications in the structure of the cortex in those who performed meditation (mindfulness), such as, upon analysing the brains of 20 practitioners of extended mindfulness meditation, along with 15 control correspondent participants, Lazar et al. (Lazar et al. 2005) established raised thickness of the cortex in the sensory region and anterior insula amongst the meditators of mindfulness, the areas that are linked with perceiving external and internal physical sensations. Moreover, mindfulness meditators had greater prefrontal cortex regions, a region involved in cognitive processing and decision-making. Holzel et al. (2010) conducted MRI research in which 26 healthy people took part in almost two months of a mindfulness-based stress reduction course. Subsequent to the intervention, participants documented a reduction in stress, which was positively associated with the grey matter density of the RT basolateral amygdala. Particularly, the 'more the level of stress reduced in subjects, [the] greater the reduction of grey matter density in RT amygdala'. These modifications in structure may act to ameliorate automatic configurations of emotional responsiveness.

Transcendental Meditation

Transcendental meditation™ applies the use of a psychologically repeated phrase or word with the aim of keeping attention on that precise object. Fundamentally,

transcendental meditation may be contemplated to be more of an emphasised attention kind of practice (Lee et al., 2004). TM is a famous style of mantra that uses traditional words from the Sanskrit language. The relaxation reaction utilises psychological reiteration of the term 'one' from the English language. A few of the practices of religious meditation may also use silent reiteration of a spiritual phrase or word (Burke et al., 2017). Besides stress-associated disorders, research has demonstrated that transcendental meditation may benefit cases of cardiovascular disorders, hypertension and high cholesterol while improving the outcomes (Thibodeaux and Rossano, 2018).

The pioneer of relaxation research, Herbert Benson, most recently worked as a professor at the Benson-Henry Institute for Mind Body Medicine at Massachusetts General Hospital. In the era of the 1970s, Benson started exploring the physiology of transcendental meditation and its effects on the practitioners of TM. At that time there were already numerous modalities for relaxation such as biofeedback, progressive muscle relaxation, hypnosis and autogenic training. TM is a practice of meditation that is performed two times a day for 20 minutes and has been demonstrated to relax the mind, as confirmed by enhanced activity of α-wave upon electroencephalogram. Some of the reports confirmed that the practice of transcendental meditation improves the functioning of hemodynamics, diminishes the activity of free radicals and reduces blood pressure (Barnes et al., 1999; Schneider et al., 1998). Now it is well identified that a lot of psychosocial and psychological interventions can have an impact on the course of a disease and the function of the immune system (Wisneski, 2017).

A team of researchers observed that a programme of transcendental meditation decreased anxiety, depression and burnout in around 20 teachers of secondary school; Anderson et al. (2008) inferred that transcendental meditation might bring about clinically significant drops in measurements of diastolic and systolic blood pressure, depending upon the meta-analytical study of approximately nine clinical studies. With regards to the practitioners of health care, Bormann in 2005 stated that mantra meditation decreased stress, anxiety and anger, while it enhanced the life quality in approximately 42 health care employees from America (Bormann et al., 2005; Lynch et al., 2018).

Spiritual Meditation

Spiritual meditation (SM) emphasises evolving a profound understanding of religious connection and explanation with excessive power. Spiritual meditation can be carried out in accordance with the practices of one of the chief spiritual traditions. Instances include thoughtful Christian prayer, Kabbalistic Jewish practices and Sufi *dhikr.* The methods used in religious meditation may be identical as in other forms of meditation, for instance, being perceptive to a meditative phrase or term, i.e. 'Maranatha'; however, the emphasis is upon religious association or insight. As few of these practices stress consideration of spiritual teachings, they may be more related to thoughtful Eastern practices versus other Eastern traditional practices of meditation, for instance, correspondence with the Buddhist Theravadan Marananussati Bhavana practice, or contemplation on one's fatality, discussed in the *Visuddhimagga* (great treatise of Buddhist practice) explanation. Some people may contemplate prayer to be a state of meditation (Burke et al., 2017) (Figure 7.4).

Figure 7.4 Spiritual meditation.

Qigong

Similar to Tai Chi, qigong was initially developed in China as a practice of martial arts, and nowadays, it is being practised as an exercise or therapy for the mind and body. Qigong means developing the essential life energy (*qi*) by utilising skills evolved by means of stable practice (*gong*). All ways of qigong merge rhythmic stationery or moving postures of the body, ways of deep breathing and determined attention aimed at giving rise to a healthy lifestyle. Mind/body/spirit balance may be acquired by combining this practice with an individual's daily routine, in spite of age, capacity or system of beliefs, in accordance with the National Qigong Association (Horowitz, 2009). In accordance with the scientists at the University of Sydney, qigong is described as 'coordination of relaxation and mild exercise by means of breathing exercise and meditation depending upon the energy meridians theory of Chinese medicine' (Oh et al., 2008). Moreover, NCCAM (National Centre for Complementary and Alternative Medicine) states that, like Tai Chi, qigong is contemplated to be a part of traditional Chinese medicine, a body and mind intervention and acknowledged energy treatment (Horowitz, 2009). Qigong varies from Tai Chi mainly in that few exercises may be performed in a lying or sitting posture (Figure 7.5).

A detailed review was conducted on numerous clinical trials on qigong; among them, seven of these research trials contrasted qigong with conventional medicinal treatment versus medicines for hypertension alone. Among them, two of the randomised control trials with sufficient data revealed improvements in diastolic

Figure 7.5 Qigong.

and systolic blood pressure, while in two clinical trials, qigong decreased systolic blood pressure considerably, contrasted with control (Lee et al., 2007). The meta-analysis of 26 randomised clinical trials from 1997–2006 establishes that, besides enhancing the number of lymphocytes and leucocytes, qigong decreased diastolic and systolic blood pressure, total cholesterol and scores of depressive mood. In one of the reviews of research data analysing qigong as a complementary therapy in cancer care, two among nine clinical trials proposed that this body-mind exercise may extend the cancer patient's life (Lee et al., 2007). Hence the reviewers recommended qigong as supportive therapy for individuals of old age with chronic diseases (Ng & Tsang, 2009).

While in a number of traditions, qigong is merely a practice of meditation, it is greatly recognised for the exercises devised by practitioners of the ancient Chinese practice of martial arts. Currently, qigong has been the centre of attention for reports regarding its relationship with the symptomatic alleviation of cancer and other ailments, and this is the feature of the method that is more commonly identified (Lei et al., 1991; Sancier, 1999; Wu et al., 1999). China has set up 'hospitals' since the 1950s particularly for the management of disorders by qigong. Specific energy treatments, also known as biofield treatments, i.e. healing touch, qigong, therapeutic touch and Reiki, have revealed beneficial effects in minimising anxiety, pain and stress; expediting the process of healing; and encouraging a considerable sense of wellbeing (Monroe, 2009; Wardell & Weymouth, 2004; Zolfaghari et al., 2012)

Effects of Meditation on Inflammatory Markers and EEG of the Brain

Meditation increases the function of the immune system by means of several mechanisms. Various research studies have demonstrated that different kinds of meditation bring about a rise in B lymphocytes and NK cells. Natural killer cells

are WBCs that target and destroy the abnormal or distressed cells, performing a role in the prevention of tumours and acting as primary protection against infections of viral origin. A reduction in these cells may give rise to the progression or development of various cancer forms, chronic and acute viral infections and several autoimmune disorders (Whiteside & Herberman, 1994). Correspondingly, B lymphocytes are accountable for the synthesis of antibodies, which strikes invading microbes, viruses and their toxins. Moreover, B lymphocytes also control homeostasis by means of healing wounds, stimulation of T lymphocytes and refusal of transplants (LeBien & Tedder, 2008). One of the pieces of research gave an electrophysiological evaluation of the influence of meditation on a sample consisting of 223 beginner meditators. Depending upon the theory of consciousness, it was speculated that participants would acquire modified states of consciousness noted in electroencephalogram data specified as changing brain wave states over each regulated meditation and outcomes endorsed these hypotheses. Current outcomes specified there was a 29% increase in theta power and an 11% rise in γ power from start to end states of meditation. The activity of α-waves in the electroencephalogram throughout the session of meditation has been involved as a type of combination in the brain that gives rise to the process of high-level cognition (Hebert et al., 2005). Another aspect of meditation-persuaded combination in the brain is frequently expressed in hypersynchronous biphasic high-frequency γ-waves, and the existence of γ-waves in the meditation is a direct verification of the combined model investigations which proposed that classifications of learning were high in the electroencephalogram machine, distinguishing pre- and post-meditation with around 97% precision. Outcomes also proposed the alteration in patterns from beta to alpha brain waves took place in a comparatively short duration. Overall effects recommended the intervention of meditation had enormous modifying effects on spectra of the electroencephalogram, and the changing speed from pre- to post-meditation states of the electroencephalogram co-spectra was considerable, hence verifying the consciousness theory. Findings propose that short-term intervention of guided meditation may provide instant and positive health benefits to assist in overcoming stress. In conclusion, future research giving an assessment of brain imaging for the training of guided meditation could give serious insights. Thus mindfulness has been recognised as a defensive factor against proactive intervention and enhances the volume of the hippocampus (Stapleton et al., 2020).

Deep Breathing and Meditation Help in Reducing Blood Pressure

According to estimates globally, high blood pressure (BP) affects nearly one billion individuals, resulting in 7.1 million ascribed deaths each year (World Health Organization, 2002). Approximately half of the adult population in the US has BP, manifested with regard to systolic over diastolic BP, in the hypertensive or prehypertensive range (American Heart Association et al., 2006; Chobanian et al., 2003). Hypertension constitutes a threat to the adult populations among all kinds of lifestyles and cultures. Hence, where persistent improvement in therapeutic management is essential, these developments must be accompanied by non-therapeutic approaches to regulate blood pressure. In relation to that aspect, MBI (mind-body

interventions), for instance, meditation, relaxation and stress management, employed alone or in combination with lifestyle changes has been estimated as prospective management for hypertension. Transcendental meditation has been researched widely as a therapy for raised blood pressure. In one of the studies, transcendental meditation brought about a considerable reduction in blood pressure almost after 12 weeks for both women and men. Another study (RCT) of transcendental meditation conducted by the same researchers stated that 20 adult patients who were managed with TM showed a 12.4 mmHg reduction in systolic blood pressure, contrasted with a 2.4 mmHg drop for people in the control group (Alexander et al., 1989).

Research analysing the outcomes of transcendental meditation on blood pressure, psychological anguish and their management among university students was also the initial RCT to show that transcendental meditation considerably enhanced coping and decreased blood pressure in relation to diminished psychological sufferings in a high-BP-risk subset. The course of transcendental meditation may lessen the threat of developing high blood pressure in young adult people (Nidich et al., 2009). In contrast, mindfulness-based stress reduction is a programme that uses the technique of stress reduction and meditation; it was initially originated by Dr Jon Kabat-Zinn.

The Center for Mindfulness in Medicine, Health Care and Society at the University of Massachusetts Medical School has managed more than 19,000 people with mindfulness-based stress reduction. This technique has also demonstrated the possibility of reducing blood pressure in people with high blood pressure. The latest research contrasting the outcomes of mindfulness-based stress reduction versus progressive muscle relaxation on pre-hypertensive people establishes that mindfulness-based stress reduction produced a considerable drop in systolic and diastolic blood pressure. Almost 4.9 mmHg drop in systolic blood pressure in the clinic was noticed in the mindfulness-based stress reduction group contrasted with 0.7 mmHg in the progressive muscle relaxation group, while mindfulness-based stress reduction produced a 1.9 mmHg drop in diastolic BP contrasted to a 1.2 mmHg rise for progressive muscle relaxation. Meditation is believed to be an intervention for high blood pressure that is possibly best distinguished as existing in its adolescence. It has evident and significant potential, with a range of research projects revealing efficiency in the short-term decrease in blood pressure identical to that acquired with single-agent medicinal therapy. On the contrary, a number of these research analyses are possibly biased because of the insufficient baseline assessments of blood pressure, lack of blinding and restricted follow-up (Goldstein et al., 2012).

How Meditation Stimulates the Immune System and Capability of the Body to Heal

Lots of research studies state a considerable impact of meditation on the management of several ailments. In patients with the human immunodeficiency virus, meditation has been demonstrated to enhance the count of T cells (Taylor, 1995), along with the activity and numbers of natural killer cells (Robinson et al., 2003). While the precise mechanisms accountable for these enhancements are unidentified, researchers propose that the stress- and depression-inhibiting effects of meditation may play a chief role. Particularly, interventions of meditation-based stress reduction have been

demonstrated to inhibit depression and negative health outcomes in healthy people (Nyklícek & Kuijpers, 2008); moreover, regular practice of transcendental meditation has been demonstrated to influence the quantity of circulating natural killer cells and B lymphocytes (Infante et al., 2014). Scientists contrasted the levels of anxiety and activity of immune cells among a control group comprising individuals that are not aware of meditation or yoga versus a group of advanced transcendental meditation practitioners; they demonstrated that the practitioners of transcendental meditation had more natural killer cells and B lymphocytes as compared to the control group. This enhances the probability that transcendental meditation could strengthen the function of the immune system, giving rise to and enhancing the capability to fight diseases and infections. Contrastingly, qigong has been revealed to decrease the number of natural killer cells while enhancing the quantity of B lymphocytes (Vera et al., 2016). One more biological marker of the constructive outcomes of meditation on the function of the immune system is the CD8+T cells activity, which are leucocytes accountable for eliminating infected and damaged cells, preventing the dissemination of cancers and viruses. These cells are identified to enhance as an outcome of vigorous exercise (Solberg et al., 1995). Throughout the duration of extensive physical stress, for instance, the stress caused by strenuous exercise, the existence of CD8+T lymphocytes in the blood is identified to escalate. Though, in the phase of recovery after long-term stress, CD8+T lymphocytes decrease below the standard while bringing about enhanced vulnerability towards infection and suppression of the immune system. Several pieces of evidence propose (Steensberg et al., 2001) that by controlling the primary CD8+T lymphocytes rise under stressful conditions, meditation therapy can decrease the period of recovery for immune suppression and hence the people's susceptibility to infection.

Likewise, meditation has also been reported to enhance the reaction of antibodies to influenza vaccine injections, in association with a rise in the stimulation of anterior, left areas of the brain hemispheres (Davidson et al., 2003). The anterior left-brain function is identified to be related to optimistic emotions (Davidson, 1992) along with a rise in the activity of natural killer cells (Kang et al., 1991). One such study showed the capability of an expert meditator to regulate their immune system after getting the antigen injection of *Varicella zoster* (a virus accountable for causing shingles and chickenpox). By means of meditation and the regulation of 'healing energies' to the injection site, the person effectively delayed hypersensitivity of skin and decreased lymphocyte reaction to the antigen of *Varicella zoster* (Smith et al., 1985). One more study on a single individual utilised two types of MBI (mind-body interventions) to assist a person recovering from an inflammatory disease named dermatomyositis, which gives rise to painful, itchy rashes and weakness of muscles. Particularly, TM and visual images were demonstrated to bring about remission by decreasing the pain and rash on the hands and improving the strength of the arm (Collins & Dunn, 2005).

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Chapter 8

Balneotherapy and Hydrotherapy

Introduction

Using water for therapeutic management is possibly as old as the existence of humankind. Till the middle of the last century, treatments in the spa, including balneotherapy and hydrotherapy, continued to be famous; however, this went into a downturn, particularly in the era of the Anglo-Saxons, with the invention of active pain-alleviating agents (analgesics). However, none of the analgesics, irrespective of their strength, is capable of easing the pain, and documentation of some serious side effects of the consumption of these drugs gave rise to a restoration of interest in spa therapy (Bender et al., 2005).

Water was utilised for healing by the ancient Romans and Greeks and is also found in biblical records. The father of modern medicine, Hippocrates, used water along with exercise, diet and herbs for healing. In his documented work on the utilisation of fluids, he stipulated the rules for the management of chronic and acute ailments by water, which were pursued by the hydropaths in the 19th century and which, along with further advancements, put water therapy amid scientific and orthodox management methods. Asclepiades, Celsus and Galen also utilised water for therapeutic purposes (Baruch, 1892). The first law regarding thermal waters, minerals and open spas was stated in 1914; however, because of the war, it was executed after 15 years. Subsequent to the Second World War, the position of health resorts and spas was controlled by the act of health promotion, subsequently identified as distinct health amenities (Golušin et al., 2014) (Figure 8.1).

Uncertainty continues to exist regarding balneotherapy and hydrotherapy. The former utilises thermal natural mineral water, gases and peloids (muds), while the latter utilises only water. Therapies in spas use several modalities for management, including balneotherapy and hydrotherapy, and make a distinctive relaxing and healing environment of their own by means of the change in lifestyle and atmosphere (Bender et al., 2005).

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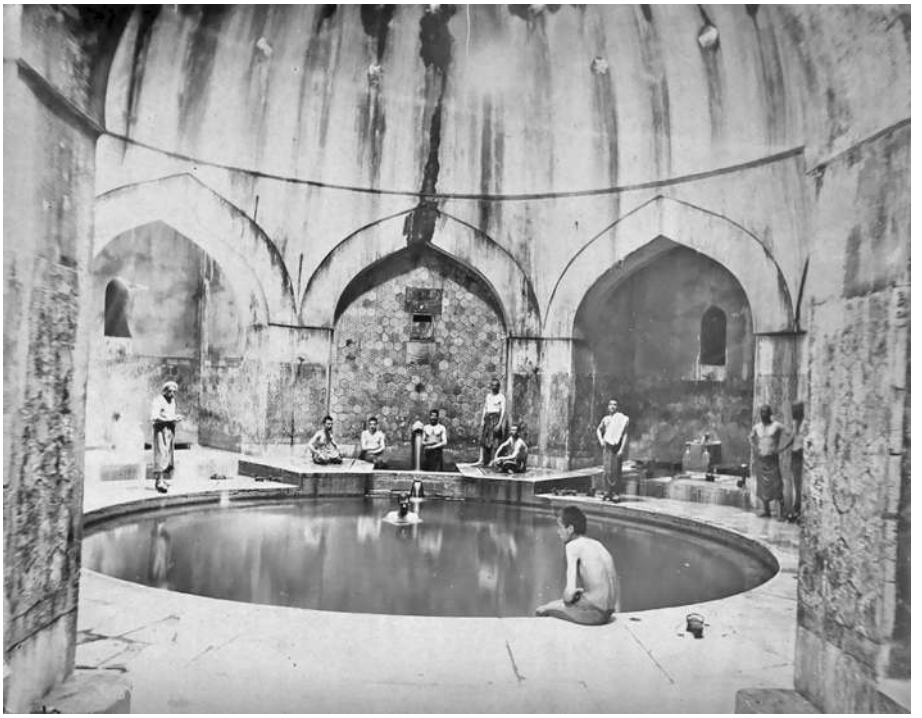

Figure 8.1 Bath of Suleiman the Magnificent in Turkey. (Source: Wellcome Collection, London.)

A Silesian peasant, Vincent Priessnitz, worked a lot to make hydrotherapy famous as compared to any other individual. He is identified as the founder of the contemporary naturopathy and nature's healing movement of the 19th century. His accomplishment was great, and he was recognised as a vigilant observer and a fine evaluator of human nature, while his technical skill supported him to discover numerous technical alterations of hydrotherapy, a number of which are still in effect today (Priessnitz, 2010).

In southwestern, central, southern, eastern and southeastern European countries, spa therapy, balneotherapy and hydrotherapy are extensively utilised and favoured by their citizens who are looking for alleviation of their symptoms, most commonly for musculoskeletal issues such as persistent pain in the lower back (Bender et al., 2005; Routh et al., 1996). Balneotherapy is described as the utilisation of baths (pools or tubs) consisting of mineral and/or thermal water from drilled wells or natural springs. Dipping in thermal water with a minimum temperature of 20°C and/or water consisting of mineral content of around 1 gram per litre is fundamental to balneotherapy (Gutenbrunner et al., 2010). On the contrary, apart from spa therapy, balneotherapy also uses other interventions, i.e. inhalation therapy, drinking mineral water and application of clay or mud at a centre or spa facility (Karagülle & Karagülle, 2004; van Tubergen, 2002). Some kinds of hydrotherapeutics are usually used in hydrotherapy, such as underwater pressure jets, showers, electric conductivity, bathing, exercise in thermal pools, as well as other non-therapeutic therapies

such as massage which can also be merged within the programmes of spa therapy. It mostly relies upon the tradition and the experience of a particular spa and typically consists of a duration of around two to three weeks (Karagülle & Karagülle, 2015).

Balneotherapy can be responsible for causing generalised and localised physiological effects, which are implemented by means of both mechanisms of the body—principally associated with heat management effects—and biological and chemical activities of the mediators (Nasermoaddeli & Kagamimori, 2005). The assimilation of biologically and dynamically organic and inorganic materials by means of the skin also plays a part in the efficiency of balneotherapy. In vivo and in vitro studies have found that both mud therapy and balneotherapy function with the help of a number of water-soluble minerals that are capable of invading human skin (Beer et al., 2003; Halevy et al., 2001; Shani et al., 1985) and appear to be the chief molecules accountable for the betterment in numerous clinical conditions. Each mud and medicinal-mineral water around the globe has several distinctive chemical constitutions and physical properties (Bálint et al., 2007; Balogh et al., 2005; Beer et al., 2003; Flusser et al., 2002; Halevy et al., 2001; Kovács & Bender, 2002; Morer et al., 2017; Odabasi et al., 2008; Sarsan et al., 2012; Yurtkuran et al., 2006). In accordance with their principal gases and ions, medicinal-mineral waters may be categorised as sulfated, carbo-gaseous, radioactive, sulfurous, chlorated, ferruginous and bicarbonated (Monasterio et al., 2016).

As far as people returning to nature, this therapy is advised and found to be effective for many health issues, including dermatological disorders, metabolic diseases, chronic inflammation of body systems, arthritis, body ache and fibromyalgia. This chapter will briefly review the traditional Roman and Avicenna's view about balneotherapy and what kind of rooms were used in the past for balneotherapy; the difference between balneotherapy and hydrotherapy; and what the medicinal benefits of balneotherapy and hydrotherapy are. Moreover, it will ask whether in the recent era spas are accurately providing the bath services that were practised traditionally.

Ancient Greco-Arabic, Roman and Turkish Bathhouses

The bathhouses of ancient times, particularly the Greco-Arabic and Turkish hammam, match up with the ones that are explained by the Romans. In the notes of *Arabian Nights*, Lane provided the following illustration of the public bathhouses (Figure 8.2):

> they consist of various chambers or rooms, along with the hard surface or footways of mosaic or chequered appearance, made up of black and white marble, blocks of fine red tile and occasionally other matter. The interior of buildings is roofed with domes, consisting of a number of rounds, small and glazed openings for the entrance of light. The initial chamber is for removing the clothes (i.e. maslakh), then the tepidarium (a transitional room consisting of tepid air) at the centre of which is a cold water fountain. Next to the walls are extensive platforms or benches covered with marble. These are equipped with cushions and mattresses for the middle and higher classes and with rugs for the lower-class people. The interior partition of the building inhabits approximately a square: the chief or central part of it is the most important chamber, the caldarium or hararah, which usually has the type of a cross. In the centre of it is a hot water fountain, emerging from a ground covered with marble, which acts as a seat. One of the facets of the

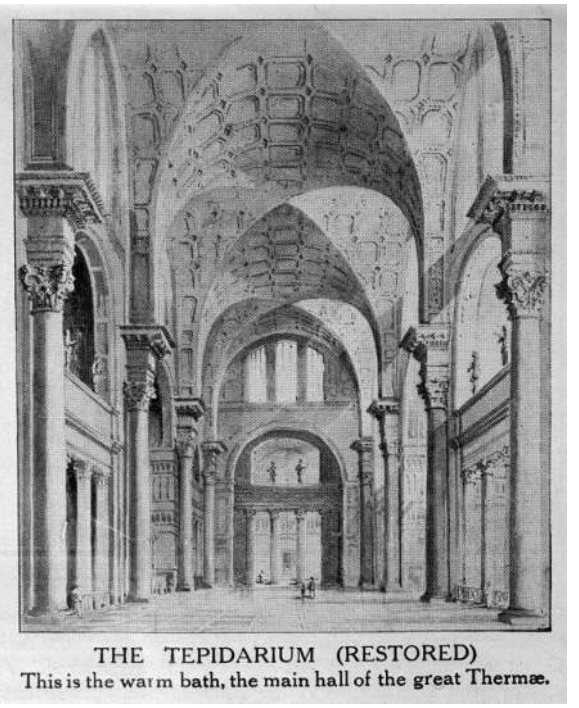

Figure 8.2 Baths of Caracalla and the Tepidarium, Rome. (Source: Wellcome Collection, London.)

> square is employed by the antechamber of the hararah (hot room). Another angle has the burning fire and the boiler above it. The third facet has a little chamber consisting of a warm water tank supplemented by a spout in the rounded vault present at the roof of the building (cf. caldarium), while the fourth facet has around two taps, one for cold and one for hot, situated side by side. A minor trough is before and underneath, which is a seat. The internal chambers are made warm by the steam emerging out from the tanks and fountains and by the fire contiguity. There is also a chamber that is utilised for removing the clothes during winter or in the cold season.
>
> (Avicenna & Gruner, 1973)

All four compartments of the hammam symbolise the four seasons, i.e. spring, summer, autumn and winter (Avicenna & Gruner, 1973; McCarthy, 2017).

> The person who wants to take baths enters the compartment of hararah by putting on shoes with thick wooden soles, one wide serviette around their pubic regions, second around their head similar to the turban, while another two covering their chest and back. The bath attendants took out the serviettes of the bather except the first one, and started crackling the joints of their toes, neck, back, fingers and other vertebral joints; wipe or clean the feet soles and massages on their body. Subsequently, the bather jumps into the water storage chamber where they are washed meticulously with water, palm tree fibres and soaps, while in the fourth

> chamber, they get shaved if they want it. After that, they come back to the antechamber, where they usually rest or lie upon a mattress, and get some light drinks or eatables, while one of the attendants again give[s] them body massage and rub[s] their feet before resuming their clothing. Throughout this resting period, a cup of coffee and pipe is consumed habitually. The procedures in the antechamber are the 'restorative friction' of the literature and of Romans and Greek baths. Prior to resuming the clothes, ointments or oils are rubbed in, while powders with good aroma are dusted upon the skin
>
> .(Avicenna & Gruner, 1973)

The ancient bathhouse or hammam is not merely a tourist or historical place, but also a significant element of socialising in Turkey. Population in this region have utilised the traditional hammam for hundreds of years to make themselves clean, preserve their health and manage a range of diseases (Kandela, 2000). Usually, moist environments like public baths and swimming pools are believed to be one of the chief spots where dermatophytes or other fungi can grow or spread rapidly (Hilmarsdottir et al., 2005); probably a person can get fungal skin infections by means of the equipment and floors of such spots. However, the hammam or ancient bathhouses has distinctive environmental characteristics like a hot room that has raised temperature, which is not appropriate for the expansion or colonisation of fungus (Goksugur et al., 2006) (Figure 8.3).

There is also significance to the decorations and pictures in bathhouses; one of the published works of Sir Thomas Arnold named *Painting in Islam* stated a number of medical authors who discussed the decorum of wall paintings and sculptures

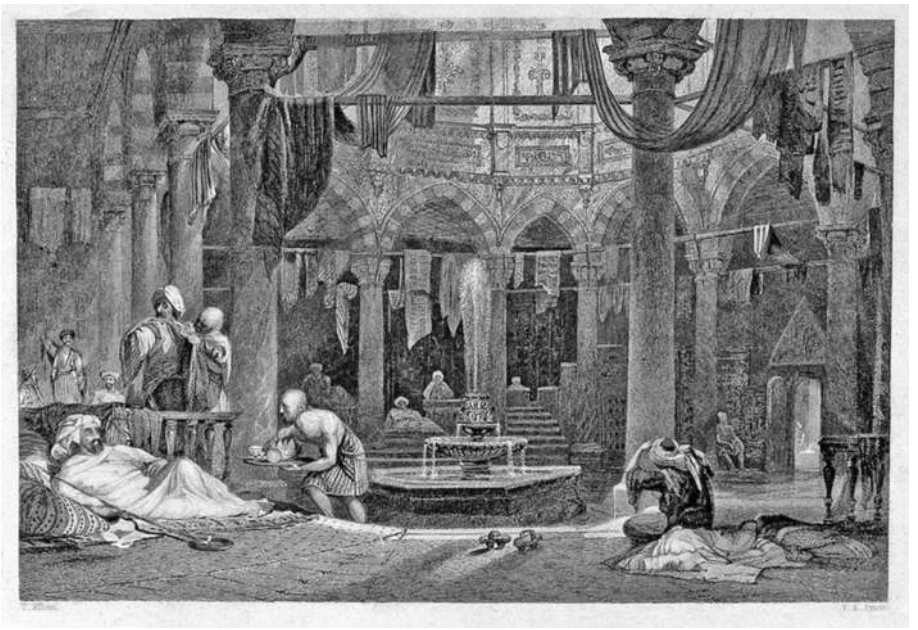

Figure 8.3 Outer cooling room of a Turkish bathhouse. (Source: Thomas Allom, 1804–1872, Wellcome Collection.)

in the restroom (Arnold, 1965). According to him, the ideal areas for bathing should consist of pictures with high-quality artistic levels and beauty, expressing beds with flowers, wild beasts, couples of lovers, galloping horses and gardens as these kinds of pictures have a strong influence on the body, either spiritual and mental (Arnold, 1965). A number of wise men, sages and physicians have acknowledged that viewing beautiful images refreshes and gratifies the soul and forces the body to leave its melancholic ideas and thoughts while providing strength to the cardiac system as compared to what any other thing can do, since it also eliminates all the evil thoughts. The pleasant colours in any beautiful portrait such as green, yellow and red are blended with a due percentage in their particular forms and give healing effects to the melancholy humours, and the worries that are stuck in the minds of humans are removed, moreover, the mind clears out the sadness and the soul gets purified (Avicenna et al., 2014; Elliot et al., 2015).

Balneotherapy

Balneotherapy is the collection of practices and techniques which is established upon scientific indication, rationally utilised and therapeutically identified medicinal-mineral waters, natural gases and peloids or muds from springs for medicinal reasons under the thermal spa facility centres. Principally, peloids are developed suspensions of mud comprised of a compound blend of adequately grained constituents of geologic derivation, mineral water and typically organic constituents from natural metabolic activity. Therefore, pelotherapy or mud therapy is one of the interventions in balneology that comprise the application of mud externally for healing purposes (Gomes et al., 2013). The term 'balneo' or 'balneum' is a Latin word, which indicates 'bath' in English. Contemporary balneotherapy is carried out by amalgamations of bathing from hot water along with sauna, outdoor or indoor exercises, inhalations, different thermotherapies, drinking, physical therapies and hydrotherapies as a compound approach. The patients who are suffering from any ailment leave their daily chores to visit the spa to get some fresh and pure air and stay there for a specific duration of time (Agishi, 2001).

Balneotherapy is a therapeutically efficient complementary therapy for the management of stress-associated disorders and low-grade inflammation. The natural ways by which dipping in medicinal-mineral water and using the mud relieve symptoms of numerous pathologies are not yet understood completely; however, it is identified that immunological and neuroendocrine reactions—comprising both cell-mediated and humoral immunity—to balneotherapy are included in these effectiveness mechanisms; giving rise to chondroprotective, antioxidant, anti-inflammatory, anabolic and analgesic effects along with neuroendocrine and immune modulation in several disorders (Gálvez et al., 2018). The temperature has a main role in the outcomes of balneotherapy, so the mud and mineral medicinal water are typically used hot as they are a remarkable medium for heat transference—capable of holding heat and letting it out gradually—therefore these managements can be considered thermo-therapeutic mediations. The distinctiveness of balneotherapy is that its useful effects are produced not merely by the physical properties of mud and medicinal-mineral water but also by their biological and chemical constitution. Balneotherapy is also believed to produce anti-inflammatory and antioxidant effects (Gálvez et al., 2018).

Health Benefits of Balneotherapy

Baths that are associated with temperature are considered an essential fragment of traditional medicine in numerous countries and cultures such as Israel, Hungary, Poland, Japan, Turkey, Spain, Romania, Austria, France, Portugal, Czech Republic, Italy, Germany, Russia, Switzerland and others, while these days thermal baths are a significant part of the public health setups in numerous countries outside and inside Europe (Gutenbrunner et al., 2010). Balneotherapy is a well-tolerated and efficient complementary approach for the management of a range of diseases—principally those associated with persistent inflammation—such as endocrine, cardiovascular, gastrointestinal, neurological and pulmonary disorders, and more significantly in rheumatic and dermatological disorders (Forestier et al., 2017; Nasermoaddeli & Kagamimori, 2005). Recently, extensive studies have documented the favourable outcomes of balneotherapy, including therapy with mud, on various clinical results in patients with fibromyalgia (Ablin et al., 2013; Evcik et al., 2002; Fioravanti et al., 2007; Ozkurt et al., 2012), rheumatoid arthritis (Brosseau et al., 2002; Santos et al., 2016; Sukenik et al., 1992), OA (osteoarthritis) (Gálvez et al., 2018) and other rheumatic disorders (Yurtkuran et al., 2006). Among all these disorders, osteoarthritis is the most frequently managed with interventions of balneology. The foremost clinical factors improved by mud therapy and balneotherapy in osteoarthritis are intake of analgesic medicines, stiffness, quality of life and pain (Espejo-Antúnez et al., 2013; Fioravanti et al., 2012). Because these therapies have minimum to no side effects, they are particularly significant for patients of osteoarthritis, who generally are of old age with multiple diseases and polypharmacy-associated risk of negative effects. In point of fact, the most recent OARSI (Osteoarthritis Research Society International) guidelines state that balneotherapy is suitable in patients of osteoarthritis with associated morbidities, for whom management options are restricted (McAlindon et al., 2014).

Effects of Peloid and Mineral Medicinal Waters on Human Health

'Peloid is a muddy dispersion or maturated mud with cosmetic and/or healing properties, made up of a compound blend of fine-powdered materials of biologic and/or geologic origins, seawater or mineral water, and commonly natural constituent from metabolic biological activity' (Gomes et al., 2013; Golušin et al., 2014). Lüttig proposed three principal categories of peloids, i.e. (i) peloid apogenes (material of peloid synthesised by mixing liquid carriers), (ii) eupeloids (undressed and original) and (iii) parapeloids (dressed, crushed and milled) (Gomes et al., 2013; Lüttig, 2006). Aside from skin disorders, peloid therapy is suggested for degenerative disorders, vasculopathy, chronic rheumatism, fractures and articular injuries (Figure 8.4).

While mineral medicinal waters are a collection of underground waters with distinct chemical and physical properties beneficial for the human body, which can be utilised for prevention and management, aluminium waters are beneficial in cases of melaena, haemoptysis, cachexia, vomiting, excessive sweating and procidentia uteri or ani. Aluminous water has a drying and cooling effect (Aegineta, 1846). Ferruginous, aerated and saline waters are useful for managing disorders originating from coldness and moisture, for the management of podagra and joint pains.

Figure 8.4 Peloid therapy.

They provide benefits in ulcers, fractures, kidney disorders, asthma and carbuncles. Ferruginous waters are also useful for the spleen and stomach. However, they must be administered progressively so as to permit the water to deeply sink into the body. Saline and nitrous baths are useful for the chest and head when body humours are persistently circulating into them; also beneficial for excessive moisture in the stomach, eliminating phlegm accumulation, swellings and dropsy (Aegineta, 1846). Some types of medicinal-mineral balneotherapy along with their medicinal uses are described in the following sections.

Radon Balneotherapy

Mineral-therapeutic waters loaded with radon are radioactive and can also be contemplated as a medicinal hormetic approach. Spa therapy with radon comprises the consumption of radon either by transdermal absorption of water-based radon or by means of inhalation. It is used in a range of inflammatory disorders such as bronchitis, arthritis, asthma and psoriasis (Erickson, 2006). However, ionising radiation (IR) has been demonstrated to be carcinogenic (cancer-causing agent) at maximum doses, while it gives rise to biologically favourable outcomes at low doses by primarily causing destruction in molecules of lower levels, which then cause the stimulation of one or more pathways of stress reaction and hence persuade adaptive mechanisms (Rattan & Demirovic, 2009) that may protect from negative health outcomes, including cancer (Calabrese et al., 2007; Feinendegen, 2005). There seems to be betterment in functions of the immune system and antioxidants along with modifications in biomarkers associated with pain (Yamaoka et al., 2004). Radon balneotherapy was found to be better with respect to alleviation of pain, improvement of functions, decline in consumption of anti-inflammatory and analgesic medicines and continuation of these effects for an extensive duration of time (Annegret & Thomas, 2013; Franke et al., 2000, 2007). Furthermore, Falkenbach and associates conducted a

meta-analysis that demonstrated a considerably better reduction in pain for a longer duration after spa therapy with radon in rheumatic disorders (Gálvez et al., 2018).

Calcium and Bicarbonate Balneotherapy

Balneotherapy with mud utilising water loaded with calcium and bicarbonate at around 38 to 42° C for one hour daily for ten days was found to be useful in patients with osteoarthritis. It decreases the levels of TNF-α, IL-6, IL-1 and other inflammatory cytokines. Furthermore, it helps reduce pain, improves physical functions and stiffness, makes the angle of knee flexion better and improves the quality of life (Ortega et al., 2017; Uzunoglu et al., 2017).

Sulfur Balneotherapy

Sulfur waters consist of several blends of water, sulfur ions and other types of ions. Sulfur waters exert valuable antipruritic, anti-inflammatory, antifungal and antimicrobial activities. The medicinal properties of sulfur water are associated with the keratolytic activities of sulfur, resulting in peeling (Matz et al., 2003). Meanwhile, on the level of immunology, sulfur-consisting waters have diminishing effects on T lymphocyte multiplicative reaction to mitogens. It has been demonstrated that sulfur waters reduce cytokine synthesis and release in skin, like interferon-γ and interleukin-2. In accordance with a few authors, these kinds of water principally act on the subset of T memory cells (Kazandjieva et al., 2008). Mineral waters consisting of sulfur are consumed for drinking as well because of their antioxidant properties (Benedetti et al., 2009). Sulfur water helps in cleansing the skin surface and is beneficial in conditions like chronic ulcers, pannus, furuncles, leprosy and vitiligo (Avicenna & Gruner, 1973).

Other Kinds of Bath

1. *Sand baths in the sun*: These baths are extremely beneficial for making the humours dry that are clogged in the skin. Such a kind of bath may be executed in different ways: a person may bury themself in sand, sit on it or sprinkle the sand on their body. The identical beneficial outcome is observed in whatever method it is executed; moreover, it alleviates pain and has drying effects on the body (Avicenna & Gruner, 1973).
2. *Shower baths, sprinkling or spraying water*: Spraying or shower baths are also beneficial. If water is sprinkled on the body, it reinvigorates the breath and vigour after dyspnoea, hot fevers and inflammatory modifications. The shower bath sprinkling or spraying of water is particularly favourable for syncope if used along with vinegar or rose water. It may reinstate the appetite; however, this kind of bath is not beneficial for the person who is suffering from cold, headaches or catarrhs (McCarthy, 2017).
3. *Oil baths*: Oil bath is useful for patients with prolonged cold fevers (particularly if there is pain associated with joints and nerves), for spasmodic conditions, for convulsions and urine suppression. These kinds of baths

> are extremely beneficial for the aforementioned disorders, while if it is combined with the flesh of a hyena, it would be an effective remedy for podagra and joint pain. Aetius also suggested mixing water with a fifth part of warmed oil to bathe as it is extremely anodyne; it alleviates nervous pain and lassitude (Avicenna & Gruner, 1973).

Hydrotherapy

Priessnitz's research laid the foundation for the efforts of Sebastian Kneipp, the popular Bavarian priest. Kneipp extended Priessnitz's research and had a wonderful impact on promoting hydrotherapy worldwide (Priessnitz, 2010).

Finally, in the first half of the 20th century, O. G. Carroll ND SP established the fundamental hydrotherapy system. He used a sophisticated approach to hydrotherapy to integrate numerous electrotherapy and physiological therapy managements. Dr Carroll was managed by Dr Ledoux in New Orleans, Louisiana, and later taught by him. Father Kneipp's hydrotherapy disciple was Dr Ledoux (Blake, 2010).

Carroll coupled electrophysiotherapy with Kneipp's concept of hydrotherapy, resulting in fundamental hydrotherapy and a recent medical approach to hydrophysiotherapy. In his widely read *My Water Cure* (Kneipp, 1896), Kneipp discusses multiple cases of various kinds of rheumatism, both local and systemic. In some situations, the body parts managed were unassociated with the area of the body that was affected, such as managing the feet, while the neck and head were the most affected (Kneipp, 1896). Kneipp's therapies covered a wide range of uses. For instance, pouring water on the upper thighs and upper body regularly, a Spanish mantle on the second day, a half bath to substitute the upper water flowing after the fourth day, and a head steam bath per week were utilised in one particular instance of rheumatism afflicting the overall body along with anxiety and feelings of suffocation. Within ten days, the patient's symptoms were alleviated (Kneipp, 1896; Priessnitz, 2010). Hydrotherapy is the internal or external application of water in any condition (ice, steam, liquid) to promote health or manage various disorders at varying durations, temperatures, locations and pressures. It is a common naturopathic modality of treatment in indigenous cultures such as in China, India and Egypt (Fleming & Gutknecht, 2010).

Cold application superficially may give rise to physiological responses such as reduction in muscle spasm, local oedema, local metabolic functions and NCV (nerve conduction velocity), contrastingly enhancing the effects of the local anaesthetic (Weston et al., 1994). Headout immersions in water for around 60 minutes in different temperatures, i.e. 14° C, 20° C and 32° C, created several impacts. WI (water immersion) at 32° C did not modify Tre (rectal temperature) and metabolic rate; however, it decreased the heart rate by 15%, and DBP (diastolic blood pressure) and SBP (systolic blood pressure) by 12% and 11% correspondingly, contrasted with control groups at ambient temperature. Along with blood pressure and heart rate, the blood levels of aldosterone, cortisol and renin were also decreased by 17%, 34% and 46% correspondingly, while diuresis was enhanced by 107% (Srámek et al., 2000).

On the other hand, immersion in water of around 20° C produced an identical reduction in plasma renin activity, diastolic blood pressure, heart rate and systolic blood pressure, despite decreased rectal temperature and enhanced metabolic rate by 93%. Concentrations of plasma cortisol inclined to reduce, while the aldosterone

level was unaffected. Diuresis was raised by 89% compared with participants immersed in water with a temperature of around 32° C (Srámek et al., 2000). In patients with CCF (congestive cardiac failure), thermal vasodilation following sauna bathing at low temperature and warm water bathing at around 60° C for 15 minutes improves cardiac function (Iiyama et al., 2008).

Temperature, immersion, upthrust and resistance all play significant roles in alleviating symptoms. In accordance with the gate theory, pain alleviation may be because of the temperature and pressure of water on the skin (Melzack & Wall, 1965). Immersing in water induced a rise in plasma levels of methionine-encephalin and, contrarily, subdued prolactin and β-endorphin-corticotrophin levels; muscle relaxation and decreased swelling of joints may also play a role. Considerable improvements in anxiety and mood may give rise to the outcomes. Reilly and Bird established that in a community swimming pool, group therapy was more beneficial as compared to the individual approach in the hospital pool. This was maybe due to focusing on the improvement of wellbeing and health rather than disease and promoting social relationships (Bender et al., 2005; Reilly, 2001).

Balneotherapy and Hydrotherapy in Fibromyalgia

FMS (fibromyalgia syndrome) is a chronic disorder escorted by somatic and cognitive indications, for instance, sleep disturbance, tenderness, chronic extensive pain and fatigue. The cause and pathogenic mechanism of fibromyalgia syndrome are still unidentified; however, biochemical, environmental and genetic factors, psychological factors, autonomic and central nervous system disorders, sleep disorders, neuroendocrine disorders and immunological disorders are believed to play a part in its development (Macfarlane et al., 2017). Many studies have documented favourable outcomes of balneotherapy on quality of sleep, fatigue, functional status, depressive mood, pain and quantity of tender points (Altan et al., 2004; Evcik et al., 2002; Fraioli et al., 2013; Kurt et al., 2016; Naumann & Sadaghiani, 2014). In one of the studies, considerable improvements were established in levels of pain, functional status, quality of life, levels of depressive mood and values of the fibromyalgia impact questionnaire (FIQ), which were involved in the ACR criteria of 2016 and utilised in the follow-up for assessing the severity of disorder subsequent of balneotherapy. Almost all of these outcomes may reveal that balneotherapy has favourable effects on the quality of life, symptoms and severity of disease and the functional status of individuals with fibromyalgia syndrome and the outcomes of oxidative stress (ÇetiNkaya et al., 2020).

On the other hand, one of the studies conducted in Brazil contrasted the management outcomes of physiotherapy vs hydrotherapy on FMS (fibromyalgia syndrome). Around 50 females in outpatient clinics were distributed into two sets. Subsequent to management for around three weeks, the group who had hydrotherapy reduced overall nap time and improved overall sleep time contrasted to the individuals getting physiotherapy (Blake, 2010).

Balneotherapy and Hydrotherapy in Dermatological Disorders

Ferdinand von Hebra, the pioneer of contemporary dermatology, was the first and foremost to observe mineral water's benefits on skin suffering from psoriasis. Louis

also discussed the significance of water baths during the management of pemphigus and ichthyosis (Nestle et al., 2009). There are inscribed reports about the favourable outcomes of alkaline waters and sulfur in the management of eczema and psoriasis (Nestle et al., 2009). It is recognised that peloids and mineral water application on the skin bring about chemical, thermal and mechanical effects. It decreases the thickness of the stratum lucidum and stratum corneum of the epidermis, enhances the number of eosinophilic granulocytes, histiocytes and lymphocytes and escalates the skin's permeability, decreases inflammation and makes the immunity and microcirculation better (Langenbruch et al., 2012).

Balneotherapy and mineral water of low solute concentration have been demonstrated to make psoriasis better without any other healing modalities. Balneotherapy has mechanical, thermal, immunomodulatory and chemical effects. A thermal hypotonic and oligometallic water, i.e. Comano thermal water, has also been assessed for its efficiency in managing psoriasis (Lee et al., 2014). The chemical constituents of this thermal mineral water, including selenium, magnesium and sulfur, are believed to have favourable outcomes on the skin. Moreover, heat may also exert anti-inflammatory outcomes (Cozzi et al., 1995).

Balneotherapy and Hydrotherapy for Back Pain and Rheumatism

In eastern, southwestern, central, southeastern and southern European countries, spa therapy and balneotherapy are used extensively and preferred by citizens who are looking for relief, principally from musculoskeletal issues including persistent low back pain (Bender et al., 2005; Routh et al., 1996). Spa therapy and balneotherapy appear to be useful in patients with lower back pain and might be contemplated as a non-medicinal treatment option for pain in the lower back. The regimen of balneotherapy was established to be considerably superior in the alleviation of pain and therapeutic improvement with regards to disability and spinal movement contrasted with baths from normal tap water (Karagülle & Karagülle, 2015).

Various types of balneotherapy, including sulfur, bicarbonate, carbon dioxide, radon, mud packs, a combination of mud packs and hot mineral baths, a combination of the Red Sea and grey sand baths, Dead Sea bath and a combination of sulfur and Dead Sea baths were identified to be beneficial in rheumatoid arthritis compared to the control group. These treatment modalities were established to be beneficial, particularly for swollen or tender joints, the strength of grip and pain. The rate of improvement varied from 5% to 93% more than the control group (Brosseau et al., 2002).

Conclusion

A range of publications has estimated the beneficial effects of hydrotherapy, balneotherapy and spa therapy against certain diseases and the short-term and long-term studies have demonstrated significant outcomes. Though several randomised controlled trials were of low quality because of the chances of bias, further trials should be conducted to analyse the effects of balneotherapy and spa therapy, especially among patients with different kinds of pain, dermatological disorders and endo-metabolic diseases. Moreover, comparative trials should also be conducted with other complementary approaches to identify their efficacy in the non-pharmacological management of certain diseases.

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Chapter 9

Circadian Rhythm

Sleep–Wake Cycle Can Influence the Immune System

Circadian Rhythm

Circadian rhythm is the combination of Latin words '*circa diem*', i.e. 'for around a day'. The term was invented by Halberg to elucidate endogenous fluctuations in organisms that were experienced in an estimated relationship with the circadian revolutionary cycles of the Earth (Conference on Photoperiodism & Withrow, 1959). It has been assessed that nearly 10% of the genome is in control of the circadian cycle (Panda et al., 2002; Storch et al., 2002). Over the last 15 years, confirmation for circadian fluctuations in constituents of the immune system has appeared, signifying that these oscillations are an essential controller of the immune system's elements with the potential to influence the commencement of disease and treatments (Arjona et al., 2012; Lange et al., 2010). Contemporary studies propose that the cyclical employment of immune cells to body tissues can influence the disease (Scheiermann et al., 2013). These rhythms are day-to-day modifications in biological activity and behaviour that come from an innate capability of organisms to position themselves with the environmental cycles. Circadian rhythms begin from an inner biological clock that initiates numerous features of human physiology, including regular fluctuations in BP, the sleep–wake cycle, body temperature and effects of cortisol in different conditions of the body and times of day (Refinetti, 2012). An increasing number of research studies and confirmation of facts establishes a relationship between fluctuating circadian timing by means of recurrent travelling in different time zones or shift work and escalated rates of metabolic syndrome, CVD and carcinoma (Haspel et al., 2020). Medical aspects of illness, for instance, worsening of asthma, increase in sensitivity of pain and MI or heart attacks are more common during specific periods of night or day (Glynn & Lloyd, 1976; Smolensky et al., 2015). The detection of the hereditary

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basis for the 24-hourly clock in the periods of 1980s and 1990s has assisted in a new period in which long-esteemed physiological circadian rhythms and scientific medicine are being reassessed in terms of cellular physiology, gene expression, signal transduction and metabolism (Huang, 2018). The National Institute of Health funded one of the workshops named 'Inadequacy of Sleep, Circadian Misalignment, and the Immune Reaction' (16–17 May 2019, Rockville, Maryland, USA). The objectives of the workshop were to underline the fundamental and clinical developments associating the biology of the circadian clock and sleep to the dysfunction of the immune system, consequently invigorating the implementation of the biological circadian clock to translational medicine.

The seminar was co-sponsored by four national institutes of health, including the NIA (National Institute of Aging), NIAAA (National Institute of Alcohol Abuse and Alcoholism), NHLBI (National Heart, Lung and Blood Institute) and NIAID (National Institute of Allergy and Infectious Diseases), considering a wide interest and identifying that sleep-based and circadian research carved across traditional regulations of academia (Haspel et al., 2020). Sleep is a natural and physiological phenomenon that demonstrates restorative and modulatory characteristics (Benington & Heller, 1995; Mackiewicz et al., 2007). The response of the immune system is controlled by three physiological processes, i.e. wakefulness, REM (rapid eye movement) sleep and NREM (non-rapid eye movement) sleep (Imeri & Opp, 2009).

This chapter will discuss the endogenous fluctuations in organisms experienced in an estimated relationship with the circadian revolutionary cycles of the Earth. Moreover, it will discuss the chronobiology, normal sleep–wake cycle, effects of sleep deprivation in humans, sleep disorders, how circadian rhythm affects secretions of hormones, how it disturbs the human immune systems and cognitive functions of the brain and how adequate sleep can enhance the immunity and productivity of a person.

History of Circadian Rhythms

Scientists started exploring circadian rhythms around 50 years ago. Though none of the research provides the determining incident from which the contemporary research in chronobiology started, experiments carried out in the 1950s on the rhythmicity of biological clocks in humans by Jurgen Aschoff and by Colin Pittendrigh using flies can be considered its starting point. The research area for sleep, which is also incorporated under the department of chronobiology to a point, developed independently, with the recognition of several stages of sleep by Nathaniel Kleitman at approximately the same time. The research outcomes of these pioneers carry on today with the development and evolution in the fields they discovered (Vitaterna et al., 2001).

The basics of the study of circadian rhythm, though, date back even further to the 1700s and the efforts of de Mairan (a French researcher), who produced and brought out a monograph explaining the regular movements of leaves in a plant. The scientist noticed that the up and down movement of the leaves carried on even when the plant was put inside a room and hence was not displayed in sunlight. This outcome proposed that the movements depicted something beyond a normal response to the light of the sun and were regulated by an internal clock.

In humans, almost all of the behavioural and physiological functions take place on a rhythmic pattern, which subsequently leads to substantial everyday rhythms in the performance capacities of humans. Whether it is involuntary (because of increasing age or any illness) or voluntary (such as shift work) situations, a disrupted circadian pattern in humans has been linked with a range of physical and mental ailments and may adversely affect productivity, safety and performance. Numerous negative effects of disturbed circadian patterns may actually be associated with disruptions in the sleep–wake cycle. A number of rhythmic actions are more influenced by the biological clock than by the sleep–wake cycle, while other rhythms are more reliant on the sleep–wake cycle. Though disrupted sleep is a distinctive feature of numerous physiological and mental diseases in humans, particularly affective diseases, it is generally indistinguishable whether the disruptions in sleep give rise to or result from the disease (Brunello et al., 2000; Vitaterna et al., 2001).

Ancient literature and authors also discussed sleep and wakefulness in great detail; Aetius stated that the favourable effects of sleep include disregarding the mental agonies, amendments of the disturbed reasoning powers and loosening of contracted tissues. The optimum sleeping time during the entire 24 hours is the nighttime since the sleepy tranquillity and humidity of night cause ideal digestion. The daytime is considered a bad time for sleeping, as in that situation, one can't sleep for a longer duration to empower the assimilation of food to be finished. The outcome is flatulence, acidity and a gurgling sound in the intestines (Avicenna & Gruner, 1973).

Chronobiology

The primary methods of the biological timekeeping structure and the possible outcomes of their non-fulfilment are among the problems described by scientists in the area of chronobiology. In its vast sense, the field of chronobiology encircles all research domains concentrating on circadian timing, including high oscillatory cycles (e.g. secretions of hormones taking place in well-defined pulses throughout the day), regular cycles (i.e. rest and movement cycles) and yearly or monthly cycles (i.e. reproductive cycles). Amid these interconnected fields of chronobiology, the areas of frequency or regular cycles are recognised as circadian rhythms. Practically all biological organisms, including fish, fungi, microbes, plants, mice, humans and fruit flies, demonstrate circadian patterns (Vitaterna et al., 2001).

Sleep

Sleep is the foremost behaviour, which is distinguished by modification in eye state and postures of the body; it is estimated dimensionally by physiological, behavioural, genetic and cellular levels of study (Buysse, 2014). Brooker defined sleep as a 'biologically modified condition of consciousness in humans and taking place in 24 hours circadian pattern'. Sleep takes place in two states: i.e. (1) with dreams (rapid eye movement) and (2) without dreams (non-rapid eye movement); both of the states are essential. Rapid eye movement sleep usually lasts from five minutes to more than one hour and takes place three to four times every night (Hsieh et al., 2013); throughout this duration, the waves in the brain are rapid with low voltage, and both respiratory and heart rates are inconsistent. Whereas during non-rapid eye

movement, both respiratory and heart rates are consistent and low, and the waves in the brain are slow, with raised voltage. In humans, there is a circadian rhythm of 24 hours, which is regulated by a chief circadian pacemaker situated in the nucleus of the hypothalamus named the suprachiasmatic nucleus (Dijk et al., 2012). Nearly 12% of cases of insomnia have impeded sleep circadian pattern disorder (Falloon et al., 2011). Occasionally, the patients who are admitted to hospitals need opioids in high doses, which causes a total lack of rapid eye movement sleep (Gay, 2010). The hospital admissions who need mechanical ventilation also face great trouble and difficulty in sleeping because of the lack of a typical circadian rhythm. Melatonin is the hormone that regulates sleep and is produced by the pineal gland; however, it is also produced in some other organs and body tissues (Hardeland, 2012).

Clocks and Immunity

Several physiological activities are controlled by internal body clocks, including sleep–wake cycles, metabolism, body temperature and feeding. Circadian activities fluctuate with a duration of 24 hours and can continue to fluctuate in the lack of entraining impetus. The clock in mammals is most frequently driven by light by means of input from the retina to the 'master clock' or hypothalamus SCN (suprachiasmatic nucleus) (Brown & Piggins, 2007). Consumption of food, temperature and other consistently changing factors can also drive circadian behaviour. Under typical 12-hour cycles of darkness and 12-hour cycles of light, ZT0 (zeitgeber time) points out the duration at which lights of the sleeping area are switched on while ZT12 represents the time at which lights are switched off. Typically, humans are most active and alert during the phase of 'daytime' after ZT0, while the animals who used to awaken at night are most active during the phase of 'nighttime' subsequent to ZT12. If the elements of the circadian clock are complete and unimpaired, mammals are capable of sustaining strong circadian oscillations in physiological processes and activity for long durations even with the lack of rising stimuli (Downton et al., 2020; Takahashi, 2017).

Recently the emphasis on circadian regulation of immune function was indicated by the observations—initially published over 50 years ago—that flowing lymphocyte numbers fluctuate regularly in healthy adults (Elmadjian & Pincus, 1946), and that the sensitivity to endotoxin relies upon the time of day it is introduced in rats (Halberg et al., 1960). Further current studies underlined the epidemiological relationships amid night shift work and raised levels of inflammatory indicators. Notably, all immune system cells and lymphoid organs experimented with so far possess biological clocks (Haspel et al., 2020). Research experiments utilising genetic testing approaches in mice and human cells proposed an association between clocks and a minimum of three basic immunological activities. The foremost reported association between immune functions and clocks are the control of secretions of pro-inflammatory cytokines, which are well-recognised arbitrators of host reactions to trauma, reactions and infections. In endotoxin-triggered macrophages, the extent of tumour necrosis factor-α secretions was established to differ in a circadian trend dependent upon the endotoxin challenge time (Keller et al., 2009).

Sleep affects the two principal effector systems, the sympathetic NS and the HPA (hypothalamus pituitary adrenal axis), which sequentially control innate and adaptive immune reactions. In the course of sleep, blood levels of epinephrine,

cortisol and norepinephrine fall (Besedovsky et al., 2012), while on the contrary, mediators that promote the growth of cells such as prolactin, growth hormones and melatonin demonstrate an abrupt rise in their blood levels. Whereas chronic sleep disruption induces activation of sympathetic NS and hypothalamus pituitary adrenal axis pathways (Vgontzas et al., 2013), which simultaneously give rise to an escalated proinflammatory and decreased anti-viral skewing of the basal transcriptome (Irwin & Cole, 2011; Slavich & Irwin, 2014).

Sleep and Wakefulness in Avicenna's *Canon of Medicine*

A moderate duration of sleep led to a balance with reference to the quality and amount of the humours; hence it has warming and moisture-preserving effects, which is beneficial especially for older individuals, who want their moisture to be renewed and preserved. For that reason, Galen said, 'each night I consume a small packet of lettuce [herbs] in combination with aromatics, the first one because it encourages sleep, while the second one because they harmonize coldness of the lettuce'. He further said, 'Now I am cautious about acquiring sleep since I am an aged man, and the sleep leads to humidity, which is advantageous for me'. A healthy individual should pay concentration to the matter of sleep: it has to be moderate, at the perfect time and overabundance must be eschewed. The finest sleep is deep sleep, and that which takes place after the food has moved on from the upper parts of the gastrointestinal tract, so that the belching and flatulence which may have developed gets diminished, in consequence of the fact that sleeping with this condition is injurious in numerous ways, even if the individual themself is unaware of it. It makes them revolve sideways in their sleep, it impedes digestion and it causes suffering; therefore, if evacuation of food from the stomach is retarded or slows down, one should have a walk, and then go to sleep. It is also abysmal to go to sleep on an empty stomach, as this is debilitating. It is also considered unfavourable to sleep during the daytime, for in this situation, disorders based on catarrhal conditions and moisture are caused to happen; the colour of health fades away, the nerves forfeit their tone; lack of vigour may be noticed, spleen gets hefty and poor appetite is observed; moreover, fevers and inflammatory conditions often show up (Avicenna & Gruner, 1973).

Posture in Sleep

The frequency of both lumbar (17.3%) and cervical (21.1%) pain has risen considerably over the past 25 years, and this is anticipated to keep rising (Hurwitz et al., 2018). Research stipulates that symptom remissions are temporary instead of for a longer duration (Croft et al., 2001; Hestbaek et al., 2006), and lumbar and cervical pain gets chronic in around 25 to 60% of cases (Manchikanti et al., 2009). Further kinds of symptoms such as annoyance and stiffness, still significant to patients, are less well investigated (Cho et al., 2013; Hodges et al., 2009). A possibly changeable risk factor that exasperates symptoms of the spine is sleep posture. Furthermore, continued nonsymmetrical postures of sleep can incite structural modifications in the spine of humans. Sleep postures have been demonstrated to be changeable (Cary et al., 2019). A few of the postures in sleep, like the prone position, are medically thought to enhance the load on the tissues of the spine, decreasing recovery

and provoking symptoms of the spine (De Koninck et al., 1992; Goldman, 2005; Gracovetsky, 1987). Another sleep posture, i.e. side-lying, is adopted by more than 60% of adults in Europe for the great part of sleep at night; side-lying emerges to be related to fewer spinal and cervical symptoms. In general, it would be useful in research for the future to verify this association and to further investigate whether a number of side-lying posture subtypes are less exasperating of spinal symptoms as compared to others. Researchers verified a trend that research participants passing excessive time in balanced side-lying posture documented fewer symptoms in the morning as compared to those in unbalanced side-lying posture (Cary et al., 2019; Cary & Collinson, 2016).

According to Avicenna's *Canon of Medicine*, the optimum way to sleep is to initiate from the right side, and subsequently revolve to the left. If an individual starts by reclining facing downwards, it immensely assists in the digestion of food, conducive to this sleeping posture; the innate body heat is intensified and conserved (Avicenna & Gruner, 1973).

Circadian Influence on Innate Immunity

Innate immunity is progressively enduring as compared to adaptive immunity and performs as the first line of defence against bacterial infections and tissue injury in the body (Medzhitov, 2008). Innate immunity is comprised of immune cells, i.e. dendritic cells, monocytes and macrophages which persistently flow in the body; the innate system of immunity utilises constant receptors to identify a broad range of infectious agents. Stimulation of these cells leads to swift inflammatory mechanism cascades that assist in suppressing infection and eventually invigorate recovery and healing (Medzhitov, 2008).

Monocytes and macrophages have been the most researched categories of cells from the perspective of circadian rhythm to date. A cause for this might be that they have a strong innate circadian clock, together with a raised magnitude of clock gene expression. This is observed, for instance, when measuring gene transcripts of the clock in peritoneal macrophages from rodents killed at unusual timings over 24 hours (Keller et al., 2009) and on cultivating macrophages from period circadian regulator 2 luciferase knock-in rodents and documenting rhythms of bioluminescence in a luminometer (Gibbs et al., 2012; Keller et al., 2009). Similarly, in other types of cells, the clock in monocytes and macrophages regulates the rhythmic appearance of a great number of downstream genes (Keller et al., 2009). Therefore, various functions of monocytes and macrophages show circadian rhythms.

Nighttime sleep, contrasting to circadian procedures, controls features of innate immunity; for instance, the nocturnal rise in activity of NK cells (a variety of cytotoxic T lymphocytes essential for innate immunity) is partially reliant on sleep. Activity and counts of natural killer cells are at their lowest during the initial segment of the night and extend to their maximum in the late hours of the morning (Kronfol et al., 1997); this nocturnal rise is diminished in individuals who exhibit disturbance in sleep (Irwin et al., 1996; Redwine et al., 2003). Circulating interleukin-6 concentrations demonstrate their highest levels two times a day, at 5:00 and 19:00 (Vgontzas et al., 1999). So far, sleep deprivation in the early part of the night delays the nocturnal rise of interleukin-6 (Redwine et al., 2000), and the deprivation of overall nocturnal sleep decreases the rise in interleukin-6 by around half (Vgontzas

et al., 1999). Lack of sleep the whole night is also stated to stimulate enhancements of inflammatory markers in circulation with proof of a dose-response in association with gradual sleep loss for more than four nights giving rise to collective C-reactive protein enhancements (Meier-Ewert et al., 2004).

Influence of Circadian Rhythm on Adaptive Immunity

Circadian elements play a chief role in controlling the dispersal of immune cells. Despite nighttime sleep, the qualities of monocytes, leukocytes and granulocytes as well as the significant subsets of lymphocytes, including cytotoxic T cells, B cells, helper T cells and HLA-DR$^+$ (activated T cells), attain their peak in the evening or in the earliest part of the night and subsequently decrease during the remaining part of the night to come to their lowest in the morning hours (Born et al., 1997). In humans, though circadian elements of blood T cells aren't dependent upon sleep and are integrated into the cortisol rhythm in this manner, the maximum levels of cortisol in the dawn period antecedes a reduction in T cells in blood by around three hours.

With respect to circadian elements, nighttime sleep plays a major role in the modulation of adaptive immune reactions. Throughout the duration of nighttime sleep, but not during the time span of nighttime wakefulness, T cell synthesis of interleukin-2 (Lissoni et al., 1998) as well as interferon-gamma (Petrovsky et al., 1998) is increased. Even a moderate quantity of sleep can enhance the synthesis of interleukin-2, as amounts of IL-2 are identical throughout a continuous and uninterrupted night sleep or partial sleep loss (Irwin et al., 1999). Nocturnal sleep also increases the synthesis of interleukin-12 by monocytes as well as by forerunner dendritic cells (Lange et al., 2006, 2010); interleukin-12 is a most important cytokine for the induction of type 1 helper T cells' adaptive immune reactions. Overall, nocturnal sleep encourages adaptive immunity, particularly during the initial part of the night when slow-wave sleep is dominant, while on the contrary, it is believed that countermodulatory procedures develop during the later part of the night when rapid eye movement sleep takes over (Irwin, 2015).

Circadian Disruption and Disease Causation

Circadian rhythms regulate the physiological processes of almost every human. Persistent disturbance of the circadian clock in shift work or throughout persistent jet lag in animal models directs the body to a greater risk of developing many pathologies. A number of these diseases in both animals and shift workers share the typical risk factors of stress, sleep deprivation and inflammation which are identified to modify the immune functions and have strong effects. Following non-traditional routines of work has been associated with enhanced risks of lymphatic (Lahti et al., 2008), breast (Schernhammer et al., 2006), colorectal (Schernhammer et al., 2003) and prostate (Conlon et al., 2007; Kubo et al., 2006) carcinomas, and additionally with stroke (Karlsson et al., 2005), stomach ulcers (Drake et al., 2004; Segawa et al., 1987), myocardial infarction, atherosclerosis, coronary artery disease (Haupt et al., 2008; Karlsson et al., 2005; Tenkanen et al., 1998; Tüchsen et al., 2006), obesity (Karlsson et al., 2001) and diabetes (Karlsson et al., 2005; Morikawa et al., 2005).

The mechanisms for these associations amid pathological conditions and exposure to shift work are not known, though it is noteworthy to observe that one typical risk factor among most of these aforementioned pathological conditions is inflammation. Shift work is a complicated lifestyle routine that, to some extent, includes sleep disruption, psychological stress, modified phase of entertainment angle and circadian disturbance.

One strong typical feature of negative health outcomes due to circadian disturbance is maybe the imperfectly regulated immune system. Modifications of the sleep–wake cycle influence the natural killer cells, the number of flowing lymphocytes and antibody titers in rodents and humans (Castanon-Cervantes et al., 2010); additionally, they escalated the inflammatory cytokines such as tumour necrosis factor-α, interleukin-6 and C-reactive protein (Castanon-Cervantes et al., 2010). Rodents that were having poor sleep demonstrated instinctively enhanced bacteraemia (Everson, 1993). Humans also showed changed immune responses subsequent to having poor sleep (Born et al., 1997; Irwin et al., 1996).

The reactivity of the immune system to different physiological conditions is well reported. As long as the immune and endocrine systems are intricately associated, the hormonal alterations in sleep distress may cause diminished resistance to infectious ailments, as observed in the animals. Moreover, insufficiency in prolactin, growth hormone, leptin, insulin-like growth factor-I and thyroid hormone, caused by lack of sleep, affects health and gives one reason for the unavailability of localisation of particular sleep deprivation consequences (Everson, 1993). Petrovsky (2001) discussed the effects of neuroendocrine factors on immune cells in great detail (Petrovsky, 2001); sleep deprivation gives rise to modifications in precise features of host protection (Entzian et al., 1996).

Maintenance of Sleep–Wake Cycle

Many years ago, supplements of the melatonin hormone became famous as a sleeping medicine; however, light has a greater influence on the circadian clock than melatonin (Czeisler et al., 1999); light at least slightly impedes sleep because it decreases the secretion of melatonin and hence reinstates the body clock. Thereby, those looking for good sleep are most likely to keep their sleeping room as dark as it could be and, certainly, keep away from midnight trips to luminously lit kitchens or bathrooms; blue light, along with its minuscule wavelength and its similarity to the light of the sky (sunlight), has the extremely potent restoring effects (Jewett et al., 1997). It is believed that the immune system consists of both membrane and nuclear melatonin receptors, and that is the reason melatonin may have an influence on the immune system (Jan & Freeman, 2004).

Nighttime sleep has a homeostatic function in immunity modulation, which is distinctive from the impact of biological processes. In one of the research series, the description of immune cell count throughout a consistent sleep–wake cycle of 24 hours has been contrasted with a 24-hour cycle of persistent nighttime wakefulness to analyse the impact of sleep in contrast with circadian oscillators on daytime as well as nocturnal immunity levels (Born et al., 1997; Lange et al., 2010). The research studies show that precise immunity aspects are primarily affected by circadian activities, while on the contrary, other measures of immunity are principally derived from sleep (Irwin, 2015).

Sleep–Wake Cycle and the Immune System

Sleep is among the most fundamental needs and biological acts in all animal and human species. After reaching 70 years of age, the average individual has spent a progressive total of around 20–25 years asleep. Rising evidence proposes that duration and quality of sleep give rise to the maintenance of health and neurocognitive function. These elements may play significant roles in the causation of diseases and death (Durmer & Dinges, 2005; Hublin et al., 2007). Sleep in humans is amazingly similar in its behavioural and physiological demonstrations to sleep in numerous other mammals. It is estimated by using muscle activity; brain activity decreases responsiveness to the environment, eye movements and body posture (Simpson & Dinges, 2008).

The relationship between the immune system and sleep was initially identified when muramyl peptide obtained by factor S or microbial peptidoglycan from the urine of humans was chemically segregated as a sleep-promoting factor in the 1970s (Krueger et al., 1984). Immunomodulatory cytokine, i.e. IL-1, a chief player in the modulation of sleep, has levels related to sleep tendency in the brain, stimulated by factor S and muramyl dipeptide associated peptidoglycans (Krueger, 2008); therefore, it is practical that sleep-modulated cytokines influence the immune system (Pandi-Perumal et al., 2007). Similarly, inflammatory regulators enhance because of persistent lack of sleep that modifies the processes of the central NS and behaviour through the feedback of the immune system to infections, as well as sleep (Dantzer et al., 2008). Therefore, during the acute phase reaction to infection or in persistent inflammation, the modulatory cytokines are divided by the immune system and sleep, including in both disrupted and physiological phases of sleep (Asif et al., 2017).

The circadian system and sleep employ a robust modulatory impact on functions of the immune system. Exploration and study of the regular sleep–wake cycle demonstrated that parameters of the immune system like the synthesis of proinflammatory cytokines and quality of undifferentiated immature T cells demonstrated their peak during early night sleep. While on the contrary, the circulating quantity of immune cells with instant effector functions, such as the anti-inflammatory activity of cytokines as well as cytotoxic NK cells, peak throughout the wakefulness of daytime. For more than the past 15 years, studies following the systematic method of neuroimmunology have collected astonishingly strong verifications that adequate sleep provides a boost to the defence mechanism of the immune system, in consensus with the famous wisdom that 'sleep assists in the healing of body'. However, the communication between regulatory networks of sleep in the CNS and cells of the immune system is fundamentally bidirectional (Besedovsky et al., 2012).

The synchronised NREM and desynchronised REM sleep cycle are continual during the night, with the extent of rapid eye movement periods rising and the extent of delta sleep diminishing. The type and quantity of sleep obtained each night also varies throughout the life course. Neonates have prolonged sleep and expend excessive time in rapid eye movement as compared to adults (healthy), though the process of ageing causes additional variations, with considerable time passed in light sleep (second stage), or wakeful in bed, with minimal time expended in the third and fourth stage of sleep (Bliwise, 1993; Weitzman, 1974). Sleep affects a wide array of physiological and behavioural functions, like cognitive potential and memory (Belenky et al., 2003; Durmer & Dinges, 2005; Van Dongen et al., 2003, 2004),

metabolism of glucose (Spiegel, Leproult, et al., 2004; Spiegel, Tasali, et al., 2004; Van Cauter et al., 1997), secretions of hormones (e.g. cortisol and melatonin), core temperature of body, renal and immune functions (Luboshitzky, 2000; Schibler, 2006), while sufficient sleep can assist in maintaining ideal levels of functions in these systems.

The lack of sleep has been established to have several effects on both physiological and behavioural functioning. Furthermore, the outcomes of sleep inadequacy are progressive, such that a slight reduction in each night's sleep can, over a time period, result in considerable functional shortfalls (Simpson & Dinges, 2008).

The studies carried out on rodents have shown that inadequacy of sleep is eventually fatal (Rechtschaffen et al., 1983); rodents subjected to continuous deprivation of sleep demonstrate disruptions in a variety of bodily, brain and behavioural functions, principally physiological systems included in the control of immunity, metabolism and thermogenesis (Rechtschaffen et al., 1989). The immunity system modifies throughout the day together with the sleep–wake cycle. Immune cells are at their peak levels in the initial time of early evening and at their lowest levels in the morning (Redwine et al., 2004). The cytokines are also at their peak levels at night (Born et al., 1997; Redwine et al., 2000). Though the reason for these diurnal fluctuations is still unidentified, it is comprehensible that disturbance of the regular sleep–wake cycle by means of sleep inadequacy can crucially affect the functions of the immune system in humans. In one experiment on critical deprivation of sleep, 64 hours devoid of sleep was related to the enhanced production of monocyte and white blood cells (Dinges et al., 1994). Moreover, levels of monocytes, granulocytes and cytotoxicity of NK cells and other active constituents of the immune system were demonstrated to rise gradually throughout the duration of deprivation together with measures of fatigue, lapses of attention and sleepiness in neurobehavioural experiments (Simpson & Dinges, 2008).

Effects of Sleep Deprivation in Humans

There has been an outburst of research on sleep and its role in the maintenance of health, with captivating verification that disruptions of sleep, including problems of insomnia and enormous duration of sleep, negatively affect the risk of inflammatory and infectious disorders and raise all-cause death rates (Dew et al., 2003; Kripke et al., 2002; Mallon et al., 2002; Vgontzas et al., 2013). These data have significant population health consequences since around 25% of the population of the US report complaints of insomnia (LeBlanc et al., 2009), and approximately 10% fulfil diagnostic standards for persistent insomnia (Morin et al., 2006; Ohayon, 1996; Ohayon, 2002), which is constantly provided for three years in almost 50% of cases (Morin et al., 2009). Certainly, disruption in sleep is a changeable risk factor: significant evidence reveals that behavioural managements have strong efficacy, along with revocation of insomnia continued in the long term (Irwin, 2015).

Sleep deprivation is partially related to enhanced vulnerability to infections of viral origins. It weakens the functions of the immune system, inhibits the release of cytokines and diminishes the cells and antibodies that fight infections. Wilder-Smith et al. analysed the impact of inadequate sleep on the immunity indicators of around 52 volunteers with good wellbeing and demonstrated its relationship with a briefly impaired proliferation of mitogen, upregulated CD14, diminished HLA-DR and differences in CD8 and CD4 (Abunada et al., 2020; Wilder-Smith et al., 2013).

Circadian Disruptions and Metabolic Diseases

While in the recent era, the duration of sleep has started to diminish, the obesity prevalence in adult humans has enhanced considerably during a similar period (Simpson & Dinges, 2008). The association between obesity and duration of sleep is closely related to the comprehension of health and sleep since obesity and its co-related physiological modifications may be a causative pathway by means of which this relationship occurs. The relationship between inadequate sleep (< 7 hours per night) and raised obesity rates/BMI levels was reported in two observational studies (Hasler et al., 2004; Taheri et al., 2004). A wide-ranging longitudinal and cross-sectional study utilising the database of the National Health and Nutrition Examination Survey (NANES) also established that people with self-reported duration of sleep < 7 hours at baseline had greater average body mass indexes and were presumed to be obese as compared to participants with seven hours of sleep duration (Gangwisch et al., 2005).

Duration of sleep > 7 hours was not persistently related to either decreased or enhanced probability of obesity; hence there is consistent proof that short durations of sleep are co-related with obesity and accompanying physiological modifications. Various biological indicators related to obesity have been researched with respect to sleep duration, including ghrelin and leptin, two appetite-associated hormones. The least duration of sleep has been established to be related to decreased leptin and enhanced ghrelin (principally a stomach-acquired peptide that invigorates appetite) in various studies (Spiegel, Leproult, et al., 2004; Spiegel, Tasali, et al., 2004; Taheri et al., 2004). Moreover, C-reactive protein levels, which have been demonstrated to be raised in reaction to lack of sleep (Meier-Ewert et al., 2004), are increased in obese people (Yudkin et al., 2000). There is assembling proof that inflammation may be associated with obesity and many diseases, such as diabetes and coronary heart disease. Since rates of obesity further rise in the USA, the likely causal association between obesity, short duration of sleep and inflammation is of importance for the health of the public (Simpson & Dinges, 2008).

Conclusion

Growing data on the association between circadian rhythm, sleep and immunity gives compelling opportunities for utilising the scientific evidence to enhance the immune system's resilience in susceptible individuals, especially shift workers, while decreasing the burden of principal inflammatory conditions of the body. A fine interpretation of how the immune system uses time as a biological variant could give rise to the development of novel therapies for stimulation of the immune system and the exact time of giving those therapies, all of which may assist in making the efficiency of present medicines better. A profound understanding may also assist in the development of procedures to enhance the efficiency of vaccines, fight infections and control serious immune reactions while associations between neuroinflammatory reflexes and adaptive immunity depict some extremely favourable research areas. Currently, there are several areas of pathology for which perception of sleep and circadian biology have yet to be considered. People must consider that circadian rhythms or biological clocks are a significant element that must be considered in prevention efforts and the diagnosis and management of diseases.

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Chapter 10

The Healing Benefits of Acupuncture

Introduction

TCM has its roots in providing strength to the philosophical basis of Taoism in an era of human history when there were no advancements in technology and no contemporary management and diagnostics for treating any diseases. A desire for better association with nature for human life preservation gave rise to further research and development (Silverio-Lopes & da Mot, 2013).

Traditional Chinese medicine (TCM) defines acupuncture as a method for harmonising the '*qi*' or energy flow, thought to circulate in body channels recognised as 'meridians' (Stux et al., 2003). In this context, any disruption in the flow of energy is a basic cause of disease. Traditional Chinese medicine suggests that there are over 2,000 points of acupuncture for the human body that are related to 12 chief and eight secondary meridians (Wilkinson & Faleiro, 2007). Subsequent to making a diagnosis, practitioners of acupuncture often cautiously choose and invigorate some of the acupuncture points by putting in the thin skin needles made up of metal and frequently operating them manually, or in a few cases, electrically. Acupuncture needles are generally made up of steel, a few centimetres in length and 0.16–0.46 millimetres in diameter (Aung & Chen, 2007). Acupuncture is utilised to manage a variety of diseases and symptoms. A number of the most frequent applications of acupuncture management are for chronic and acute pain, particularly of the back, elbow and knee, adverse reactions to chemotherapy and for managing fibromyalgia and osteoarthritis (Cao et al., 2012; Choi et al., 2012; Deare et al., 2013; Hopton & MacPherson, 2010) (Figure 10.1).

While numerous research studies acknowledge the acupuncture theory of traditional Chinese medicine, the focus has been placed on recognising molecular and cellular signalling pathways that may be experimented with in research design. For instance, modern discoveries propose that a number of the clinical outcomes of acupuncture may be associated with local responses to inflammation, secretions of adenosine, endogenous synthesis of opioids, cytoskeletal remodelling, neuromodulation

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Figure 10.1 Needle insertion in acupuncture therapy.

and tone of the autonomic nervous system (Carlsson, 2002; Goldman et al., 2010). Probably an association was found between the stated biological cascades stimulated by activating the acupuncture point and the balancing movement of *qi* in the body (Langevin et al., 2006; Takahashi, 2011).

One of the first documents to systemically discuss acupuncture's utilisation in managing human diseases by means of the movement of *qi* in the meridians is recognised by the name of 'Ling Shu', which is the second module of an ancient Chinese medicinal textbook named *The Yellow Emperor's Classic of Internal Medicine* (English title). In the foremost part of the book, Su Wen discusses the management strategy of TCM (Unschuld, 2016).

Historical Aspects of TCM

The primaeval traditional Chinese medicine was associated with beliefs that the ancestors who have died were capable of jeopardising or even devastating a human's life, and the practices of healing attempted to reinstate not merely the living but also the demised. With the end of ancestral medicine, supernatural, demonological or magical beliefs became the reason for developing all disorders. The most distinguished developmental era of traditional Chinese medicine was throughout the Han Dynasty. At this duration, the intellectual Chinese upper class initially tried to classify the phenomena into a bounded amount of causes and outcomes. From this point, the health care of the Chinese people took a determining turn (Loewe, 1994). Laws of nature explicated in doctrines like yin-yang theory and the concept of five elements were applied to describe health and illness and compose preventive and management approaches. Although Han medical experts manifestly contemplated earlier concepts of ancestral and demonological impacts on the health of humans, in contrast, their theories were more logical. However, Chinese medicine interrelated and coexisted with ancient health care interpretations from that time onwards. But Han Chinese theories were not generally ubiquitous, consistent or approved. For instance, one Chinese school of thought divided the two yin and yang classes into four subclasses of yin and yang, while on the other hand, the second Chinese

school advised three subclasses of both yin and yang. Meanwhile, both of these Chinese schools of thought, despite having contradictory beliefs, emerge to have the same opinion regarding the 'five phases' doctrine rejection that is significant for other Chinese medicine theories (Unschuld, 2010). With the passage of time, two distinct traditions of health care and medicinal texts emerged in China (post-Han). Literature about prescriptions and pharmaceuticals was developed and used without recommendation to what has been explained as concepts of systematic connection. Contrastingly the literature on moxa cautery and needling that developed gave details about those concepts. Another significant factor of traditional Chinese medicine and acupuncture's success has been the theory of '*qi*'. Though the notion of vapours (invisible agents) that are accountable for preserving health and life is not completely Chinese, in fact, it is one of the principal ancient medicinal concepts of almost every culture; for instance, Erasistratus and Praxagoras (the Greek physicians) theorised that arteries don't conduct blood. Still, they carry the vital forces, i.e. pneuma (Prioreschi, 1996).

Yin and Yang

Yin and yang, also recognised as Tai Chi (paramount principle of life), included 'The two active powers' (the black part represents yin while the white part represents yang) both existing in between and from which a vigorous and coordinated force is created. Each of the yin-yangs consists of the other's seed; there is a little circle of seed from yin incorporated in the white space of yang; similarly, the circle of seed from yang is contained in the yin. The outstanding yin and yang symbol emerges like a fish pair revolving around or encircling each other; the head of one creates the tail of the other. It demonstrates that yin and yang are derived from each other and modified into each other.

The force Tao circulates through all living beings. Each individual has to nurture the vital energy or *qi* (an essential force of life) that has been bestowed on them. There must have an equilibrium between everything in this universe. Male (yang) and female (yin) forces are working every time, and there should be a perfect balance among them; furthermore, extremes of anything should be avoided. In the morning, when yang energy is at its abundance and peak, an individual gets active naturally; in that way, if people are consuming their energy, they start feeling tired, and they require to harmonise the yang with yin (taking naps or some rest) throughout the day so that they can preserve the level of their energy (this gets extremely true especially when a person started getting old). On the contrary, the yin energy gets high or abundant in the evening (Low & Ang, 2010).

The classical notion is generally considered as a life force or vital energy. If an individual is in 'better health', it signifies that energy yin and yang are in equilibrium, and then the flow of *qi* is smooth. While if yin and yang forces get out of balance, there must be some disruptions in *qi* which give rise to disease and ill health (Wang et al., 2008).

In accordance with the yin and yang theory, *qi* is the most fundamental element that, besides cosmic makeup, is everything in the world. It is the beginning of the world and the basis of matter for the integration of the limitless diversity of everything globally. Moreover, it is the foundation of the integration of the spirit and body. Yin-yang is the innate characteristic of *qi*; the association of yin-yang with *qi* is

the basic cause of self-movement in *qi* and the essential cause for the modification of everything. Yang modifies *qi* while yin transforms into configuration; *qi* (intangible) and form (physical), and their shared transformation is the simple kind of the physical world that exists (Qi Cao, 2018).

Concept of *Qi* and *Qi* Deficiency Syndrome

The fundamental concept of health in TCM comprises the *qi* (vital energy of the body) unidirectionally circulating by means of the meridians (compound channels of network) just below the skin, though also flowing inside the blood vessels. It penetrates the tissues and organs and supports all physiological functions. Health is the constant and balanced flow of *qi*, and sickness follows when there is any disturbance in the *qi* flow. The components that can have an impact on the flow of *qi* include trauma, malnutrition, anger, anxiety, fear, hereditary factors, stress, grief, weather conditions and infections. By introducing needles, the acupuncture practitioner tries to restore the balance between spiritual, emotional and physical aspects of the person and to make the quality and flow of energy better (Zijlstra et al., 2003). Acupuncture points are particular points along the channels at which *qi* can be retrieved and rebalanced.

Approximately 365 points are present around and along these channels, which could be prompted to rectify the imbalance and reinstate the body to a healthy state; these points are known as acupoints (Cantwell, 2010). Several researchers believe that if some organs of the body are influenced by disease, sensitising the acupoint has the ability to exert strong functional modifications, reflecting the specificity of acupoints (Rong et al., 2011).

The *qi* homeostasis quite resembles the allostatic load in the area of stress medicine. If *qi* becomes imbalanced or diminished, then emotional, mental and physical dysfunction can take place. When there is extremely low or extremely high *qi* in a provided channel or when the *qi* is blocked or stagnates, it can cause physical illness. In the most fundamental words, acupuncture management comprises introducing ultrathin needles at several body points, recognised as gateways, to rebalance or unblock the *qi* flow. As a matter of fact, techniques of acupuncture can enclose an extremely wide variety of techniques for activating *qi*, including electromagnetic fields, laser light, electrical current and moxibustion (burning of powdered *Artemisia vulgaris* leaves to provide warmth). Studies in the era of the 1970s and 1980s connected acupuncture analgesia to the elaboration of endogenous opioids, especially endorphins. In 1995, needles of acupuncture were no longer categorised as 'experimental' by the USFDA (Wisneski, 2017).

QDS or *qi* deficiency syndrome is extensively found in people of middle age or in older adults. In the Chinese theory of classical medicine, there is a close association between common ageing symptoms (external) and deficiency of *qi*. As a core concept, ageing is identified as the result of *qi* deficiency (Zhang et al., 2015).

From the aspect of contemporary medicine, ageing is related to a broad range of chronic ailments in humans, including cancer, diabetes, neurodegenerative and cardiovascular disorders (Brunet & Berger, 2014; Kendig et al., 2014). The mechanism of biological ageing is complex and may emerge from different severe causes, including destruction or deterioration of the cells in several organs by means of infections and mutations, intoxication or damage from radiation, and the inability of the body to eradicate hazardous waste products (Eyring & Stover, 1972).

The notion of sub-health has gained attention from both the general public and health practitioners in China, principally because it depends on the theory of traditional Chinese medicine. A total estimate of prevalence demonstrates greater than 60% of *qi* deficiency syndrome in China takes place with rising age (Zhang et al., 2015). There is an apprehension that serious social and public health issues may arise if the alarming symptoms and signs of sub-health are not identified and managed. An outcome of unmanaged sub-health gives rise to chronic ailments, including diabetes, stroke, cancer, chronic pulmonary ailments and cardiac disorders, which, as the emerging causes of fatality, represent 63% of all mortalities globally. There has been a progressive rise in the frequency of chronic disorders, with a death rate of greater than 85% of all fatalities in China every year. Moreover, 91.7% of Chinese adults above 60 years or older are influenced by chronic ailments, and 55% have greater than three parallel uninterrupted conditions (Zhang et al., 2015).

How Acupuncture Works

Insertion of IM needle and excitation causes a certain afferent activity pattern in peripheral nerves (Kagitani et al., 2005). Different types of fibre, thin myelinated (Aδ), thick myelinated (Aβ) and thinner C fibres (unmyelinated), have all been documented to be activated by stimulation caused by acupuncture needles (Sato et al., 2002). Subsequent to insertion, the needles of acupuncture can then be triggered by electrical (electroacupuncture) or by manual stimulation for around 20 to 40 minutes. In the case of electroacupuncture, needles are connected to electrodes for the passage of electric current. It has been proposed that around 1 to 15 Hz (low frequency) electroacupuncture along with recurrent contractions of muscle stimulates physiological pathways identical to those resulting from contraction of muscle during physical activity (Andersson & Lundeberg, 1995; Kaufman et al., 1984).

Activation of acupuncture points in muscular tissues gives rise to peripheral secretions of some neuropeptides like NGF (nerve growth factor), CGRP (calcitonin gene-related peptide), substance P and VIP (vaso-intestinal peptide) from peripheral nerve endings into the adjacent areas. The outcome is enhanced uptake of glucose and skeletal muscles microcirculation (Higashimura et al., 2009; Sato et al., 2000) depending on the location and number of acupuncture needles and the type and intensity of stimulation. Activation of the afferent muscle also regulates the signal transmissions in the central nervous system and the spinal cord (Stener-Victorin et al., 2008). Acupuncture at the spinal level may regulate the organ functions (e.g. heart, ovaries and urinary bladder) situated in the area of similar innervation as the stimulated points of acupuncture through sympathetic reflexes (Sato et al., 1997).

The nervous system, at the same time, transmits signals to the brain, which brings about a reaction that may further impact the organ. Both central and spinal acupuncture mechanisms possibly contribute to the overall outcome of acupuncture management. Since the central nervous system controls the secretions of pituitary hormones, acupuncture may also regulate the endocrine system, which may successively affect the SNS (sympathetic nervous system) activity. Particularly, low-frequency electroacupuncture gives rise to the secretion of a huge quantity of oxytocin, serotonin, neuropeptides and endogenous opioids in the central nervous system, which appears to be necessary for persuading functional modifications in various organs (Andersson & Lundeberg, 1995; Han, 2004;

Stener-Victorin et al., 2008)—principally, an endogenous opioid, β-endorphin, which has great attraction for the μ-receptors (Basbaum & Fields, 1984). The system of β-endorphin has a modulatory role in a range of functions, including autonomic activities (Andersson & Lundeberg, 1995; Eyvazzadeh et al., 2009). β-endorphin is a chief regulator of functional autonomic modifications like outcomes on the vasomotor centre, which gives rise to a general reduction of sympathetic tone, demonstrated as modulation of BP and as inhibited muscle activity of the sympathetic nerve (Andersson & Lundeberg, 1995; Yao et al., 1982).

Acupuncture Point Selection

Traditionally acupuncture has been used to treat several disorders, including pain in the lower back region (Berman et al., 2010; Lim et al., 2018), post-stroke rehabilitation (Chavez et al., 2017; Lee & Lim, 2016) and hot flushes of menopausal age (Avis et al., 2016; Chien et al., 2017). Currently, people are progressively taking more interest in acupuncture for the management of several disorders, and the number of acupuncture practitioners is also rising (Fan & Faggert, 2018). As with other management, selections of acupuncture points vary in accordance with the disease type. A number of acupuncture point selections are often advised or used for particular diseases (Borud et al., 2009; Kwon et al., 2016). For instance, LR3, K17, SP6, CV4, LI4, HT6, LU7 and K16 are frequently used for the management of hot flushes in postmenopausal age (Borud et al., 2009). BL34, BL25, BL33, BL24 and BL31 are generally used for the management of lower back pain (Lee et al., 2013). At the same time, selections of acupuncture points can differ even for the same kind of disorders (Kalauokalani et al., 2001; MacPherson et al., 2004; Napadow et al., 2004). There are various theoretical components in acupuncture points of traditional acupuncture theories, such as distant or local effects of points, eight meeting points, source points and five transport points. Each of the elements postulates diverse facets of *qi*, meridians, bowels and viscera (Jang et al., 2021). These variations in theories could have an impact on the different practising styles of acupuncture (Yu et al., 2015)

Acupuncture in the Management of Various Disorders

Churchill's authentic elucidation consisted of a number of cases of his own along with a few other sources; in a follow-up to his monograph, he discussed a number of fresh cases in 1828. He illustrated two individuals with acute severe pain in the back who got relieved instantly by the needle insertion in the muscles of the lumbar region, and two females with 'rheumatalgia' who were unable to respond sufficiently to therapeutic management but were treated by the needle insertion in the intercostal muscles (Churchill, 1828).

Acupuncture for Rhinitis

Management by acupuncture is common among people with rhinosinusitis and asthma and hence should be considered by health care providers (Blanc et al., 2001; Schäfer et al., 2002). In children, acupuncture resulted in improvement of recurrent

frontal and chronic sinusitis (Pothman & Yeh, 1982), making the allergic rhinitis less severe by using the head points of acupuncture which are established to be efficient in a study including 102 patients. Subsequent to two years of follow-up, a considerable number (72%) of people demonstrated a therapeutic effect, principally reflected by decreased skin swelling and redness diameter (Zhou & Zhang, 1991).

Acupuncture in the Management of Pain

Generally, acupuncture is used to manage pain in contrast with any other clinical indication, principally migraine, lower back pain, neck pain, headache, shoulder pain and knee pain (Hopton et al., 2012). Nearly 50% of patients with persistent pain get prolonged relief from an acupuncture course in clinical setups. Approximately 35 acupuncture experiments for the management of persistent low back pain were reviewed by Furlan et al. (2005), who documented that there is verification of functional improvement and alleviation of pain with acupuncture and that it enhances the efficacy if combined with conventional management (Furlan et al., 2005). Moritz et al. (2011) evaluated 1,005 cases of lower back pain managed with acupuncture and established around 49% decrease in visits to doctors after the acupuncture with a following 37% reduction in the cost of health care services for people who have gone through the acupuncture therapy contrasted to 2% of the people receiving routine care (Moritz et al., 2011).

The American Pain Society and American College of Physicians in the USA have issued guidelines (Chou et al., 2007) that encourage acupuncture use for lower back pain. In one of the meta-analyses and systematic review of 14 randomised controlled acupuncture trials for neck pain, researchers described that acupuncture had been demonstrated as considerably beneficial in the short term; however, there was inadequate proof for determinations as to its prolonged outcomes. The study by Vickers et al. (2012), the only major study of high quality on acupuncture for the management of neck pain, had 3,118 participants, and the outcome demonstrated an extremely substantial effect size of 0.68 for acupuncture in contrast with general care (Witt et al., 2006). The commonly used acupuncture points for neck pain are SI14, BL10, GB20, GV14 and GV21 locally, whereas distant points are LR3, LI4, TE5, GB34, BL60 and SI3.

Large-scale experiments started by German health insurance companies on tension headache (Melchart et al., 2005) and migraine (Linde et al., 2005) both demonstrated semi-regulated acupuncture to be more efficient in contrast with no management but identical to minimal acupuncture or placebo. Sun and Gan (2008) issued a well-conducted systematic review of around 31 studies for the persistent headaches of both categories and deduced that acupuncture is better than medication or placebo in improving the frequency and intensity of headaches. Two of the Cochrane studies cover this section: the first one for migraine, which discussed 22 clinical trials and deduced that there are persistent verifications for acupuncture usage for prophylaxis and in acute attacks. The review on tension headaches involved 11 clinical trials and documented that acupuncture is a useful approach for tension-type headaches (Linde et al., 2009a, 2009b). In 2006, White and Kawakita studied the evidence regarding acupuncture for osteoarthritis of the knee and proposed recent verifications that acupuncture is expected to be a substitute for non-steroidal anti-inflammatory drugs, being at least efficient to the same extent and possibly much safer and more economical (White & Kawakita, 2006).

Liu et al. (2010) analysed 12 randomised controlled trials of acupuncture for the management of trigeminal neuralgia and deduced that the evidence, even though of inferior quality, proposes that acupuncture is valuable management with identical benefits to carbamazepine but with minor adverse effects (Liu et al., 2010). There is some proof that acupuncture is useful in both HIV and diabetes-related peripheral neuropathy (Shiflett & Schwartz, 2010; Zhang et al., 2010). Research-based studies on painful diabetic neuropathy by American academies propose that stimulation of electrical nerves percutaneously should be contemplated for alleviation of pain (Bril et al., 2011). In 1998, the National Institute of Health of America advised that acupuncture should be incorporated into an extensive programme for the treatment of fibromyalgia. This appears to be a practicable approach, as acupuncture is identified to enhance the release and synthesis of noradrenaline and serotonin (Han, 1986), both of which are considerably inhibited in patients with fibromyalgia (Hayhoe, 2011); in fact, the merger of medicines, especially amitriptyline (the most famous drug to manage fibromyalgia), with acupuncture is believed to be synergistic (Fais et al., 2012).

Role of Acupuncture in Immunity

To perceive the matter of immunity from the viewpoint of traditional Chinese medicine, it is essential to recollect a few concepts that will be discussed here. For traditional Chinese medicine, the idea of health is the balance between yin and yang or a precise flow of energy movement in the body. Sequentially yin and yang are described as segments of contradictory and complementary aspects of nature and associated with each other. There are several types of etiological factors causing pain; however, the principal pathology is either because of the obstruction or impediment or deficiency of vital energy. The fundamental statement regarding pain, created around 2,000 years ago, states that 'if there is no impediment in the free flow of blood and energy, then there would be no pain; but, if there is any disturbance in the flow of energy and blood, the pain starts to develop'. The flow of blood and *qi* in the body should be persistent, similar to the uninterrupted courses of the moon and sun. In TCM theory, it is advised that acupuncture can make the human body stronger to withstand diseases by inserting needles into specific points. Extensive research has demonstrated that acupuncture can modulate immunity, for instance, to increase antistress and anticancer functions of the immune system and demonstrate anti-inflammatory effects. Zusanli or ST36 is one of the acupuncture points that is extensively used in immune-associated ailments. Electroacupuncture at ST36 (Zusanli bilateral points) prevents the immune barrier of intestinal mucosae from sepsis (Liang et al., 2015; Pan et al., 2021).

Zhu et al. (2015) stated that preconditioning electroacupuncture at acupoint ST36 evidently mitigated cecal ligation and puncture induced intestinal lesion and extensive permeability, at the same time demonstrated preventive outcomes on the immunity barrier of intestinal mucosae by enhancing the sIgA concentration and the percentage of CD4+, CD3+and γ/δ T cells and the CD4+/CD8+ratio of T cells, which ultimately diminished the death rate by sepsis (Zhu et al., 2015). Acupuncture and moxibustion improve the symptoms of Crohn's disease by controlling the equilibrium between T regulatory and Th cells in the mucosa of the intestines. Zhao et al. presented verification from RCT that acupuncture and moxibustion controlled the

Th17 and Treg cell ratio in the mucosae of the intestine among patients with Crohn's disease and reinvigorated the equilibrium amid the subsets of immune cells, giving the basis for clinical usage of management for Crohn's disease (Zhao et al., 2015).

In TCM, several acupoints are believed to have an impact on the immune system. In the west, scientific literature has given limited data from studies on experimental animals with respect to prospective immunity-boosting outcomes of acupuncture; however, further research is essential (Filshie et al., 2016). The acupuncture mechanisms may regulate immunity, and this is similar to that of average exercise in which enhanced activity of natural killer T cells has been established (Jonsdottir, 1999).

Role of Acupuncture in the Management of Cancer and Its Associated Symptoms

A great percentage of cancer patients suffer from serious pain in spite of suitable titration of co-analgesics and analgesics. The adverse effects of these drugs can become enormous, and several patients want to try non-pharmacological treatment like acupuncture to assist in regulating the symptoms. Acupuncture is applied to manage pain in patients of cancer initiated by the ailment itself or, more frequently, an outcome of one or more of the following treatments like chemotherapy, radiotherapy and surgery. In one of the surveys in patients with breast carcinoma, a decrease in distress, pain, lifestyle interference and depression was observed (Filshie et al., 2016). Numerous RCTs (randomised controlled trials) have demonstrated acupuncture's role in the treatment of pain in cases after several cancer-associated surgeries (Mehling et al., 2007), including pain post-gastrointestinal and post-thoracotomy surgery (Kotani et al., 2001; Wong et al., 2006). Potential analysis of 20 patients with cancer-associated dyspnoea at rest demonstrated significant improvement symptomatically in around 70% of cases and considerable improvement in individual scores of anxiety, relaxation and breathlessness in around 1.5 hours (Filshie et al., 2016).

Conclusion

The contemporary therapeutic variety of acupuncture is possibly the category of unconventional treatment that has acquired an extreme degree of therapeutic acceptance. This is enormously due to the fact that significant research studies can be found to demonstrate that needle insertion has noticeable physiological outcomes. This gives a foundation for further research that acupuncture has remarkable effects in the management of certain conditions of the body, and it is a genuine neurophysiological approach. However, its local and systematic effects are still needed to be identified in broad dimensions so that its synergistic and antagonistic effects with other therapies and medicines can be verified.

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Chapter 11

Autoimmune Diseases and a Multidisciplinary Approach to Cancer

Introduction

The immune system in humans has a compound network of a variety of dynamic cells exhibiting a comprehensive range of receptors that work together to react to infections, eradicate pre-cancerous cells and preserve metabolic health. Failure of this delicately composed immune reaction is particularly limiting to the duration of life, and even fine modifications in its capability to differentiate an attacking infectious agent from the host can cause a range of autoimmune disorders. Certainly, autoimmune ailments have an impact on around 5 to 8% of the global population and give rise to great suffering for patients while also demonstrating a huge socioeconomic issue globally (Fugger et al., 2020).

Although believed to be rare, over 80 autoimmune disorders have been recognised to date, including type 1 diabetes, rheumatoid arthritis, autoimmune hepatitis, multiple sclerosis and primary biliary cirrhosis (Wang et al., 2015). Environmental (hormones, xenobiotics, nutrition and apoptosis), epigenetic and genetic factors act as predisposing factors for the development of autoimmunity (Bolon, 2012). Some autoimmune disorders that have systematic effects, such as rheumatoid arthritis, psoriasis and systemic lupus erythematosus, are initiated as an outcome of the interaction of several autoantigens, including molecules of cellular surface and matrix proteins inside the cells along with responsive autoantibodies. Moreover, some particular diseases, including inflammatory bowel disease, type 1 diabetes, Hashimoto's thyroiditis and multiple sclerosis, can also take place because of the immune reaction to autoantigens confined within a specific organ. The existence of autoimmune disorders may have an impact on the development of other persistent disorders. For instance, patients with persistent inflammatory ailments (such as rheumatoid arthritis and systemic lupus erythematosus) are at more risk as compared to general people for developing particular forms of lymphoma (Hansen et al., 2007).

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The connection between the development of cancer and autoimmune disorders is bidirectional. On one side, an enhanced risk of cancer development, both non-haematological and haematological, has been noticed in various autoimmune disorders, while in contrast, a number of malignancies may enhance the risk of autoimmune disease development (Giat et al., 2017).

Contemporary and common management alternatives for autoimmune disorders include NSAIDs (non-steroidal anti-inflammatory drugs), analgesics and glucocorticoids (Konforte et al., 2012), though, in the current era, medicinal immunosuppression and biological mediators have also been demonstrated to be useful in the treatment of autoimmune diseases (Alexander et al., 2015). There is inadequate knowledge regarding the causative factors of various autoimmune disorders. Hence, the recent clinically significant treatment is based on the symptomatic treatment and regulation of disease to decrease the number of relapsing incidents (Loma & Heyman, 2011; Mavragani & Moutsopoulos, 2014; Pickup, 2012) till the identification of efficiently targeted treatments. An example is the insulin application for patients with type 1 diabetes mellitus to preserve the homeostasis of blood glucose (Aletaha, 2002; Loma & Heyman, 2011; Mavragani & Moutsopoulos, 2014) or the utilisation of saliva and tear substitutions as the principal treatment for the patients of Sjogren's syndrome, accompanied by complementary drugs to manage extra complications. IFN-β (interferon beta) is also extensively utilised in the treatment of multiple sclerosis (Hegen et al., 2015), though these biological medicines are only beneficial in a few patients (Targan, 2006).

The biologics (e.g. anti-TNF-α antibody) and the NSAIDS represent an eminent category of such medicines, though the consumption of these medicines is related to severe side effects, including cardiovascular problems and gastrointestinal bleeding. Owing to the adverse effects and the extreme price of conventionally consumed anti-inflammatory medicines, patients with arthritis are progressively switching towards the modalities of complementary and alternative medicines for the management of ailments (Venkatesha et al., 2011). Yet, while reducing the inflammatory progression or symptoms of disorders, overall treatment rests elusive. Herbal medicines and natural diet-based products are also researched extensively as prospective management strategies for autoimmune disorders (Khan et al., 2019). This chapter will briefly discuss a few most commonly observed autoimmune disorders and their management with the traditional system of medicines. At the same time, a multidimensional approach including nutritional and other CAM modalities will be discussed in the context of oncology for the prevention and treatment of a range of cancers.

Pathophysiology of Autoimmune Diseases

Autoimmunity is caused by the uneasiness and abnormality of the human immune system, which gives rise to pathologic and extreme responses from adaptive and innate immunity against organ-precise self-antigens, consequently ensuing in dysfunction and destruction of tissues by means of inducing injury and inflammation in the systems that are affected (Davidson & Diamond, 2001).

The hyper-stimulation of the innate immune reactions and failure in selecting the range of T and B cells or failure to control stimulated T and B cells can elicit the beginning of autoimmunity in individuals who are susceptible. Additionally, the

existence of autoreactive T and B cells many years prior to the appearance of actual disease signifies that multiple factors could function in a sequence to elicit the disease (Davidson & Diamond, 2020). Inflammations in autoimmunity are directed by similar associations between self-reactive T cells and APCs (antigen-presenting cells) (Mackern-Oberti et al., 2015). Hence the principal reason for autoimmune management strategies is to encourage tolerance by means of targeting antigen-presenting autoreactive cell associations. In spite of the indispensable role of dendritic cells and probably macrophages, particularly in the initial stimulation of autoreactive B and T cells, verifications propose similar associations of T/B cells are essential on this occasion. A number of studies by means of eradication of T lymphocyte populations, utilising anti-T cell immunoglobulins and/or thymectomy, have demonstrated the essential roles of biological immunity in causing a number of autoimmune disorders manifested by the production of autoantibody, and the dysregulation of B cells is thought to play a chief role (Hang et al., 1984; Wofsy et al., 1985).

Comprehensively, affected organs and these mechanisms by means of autoimmunity differ extensively. For instance, in multisystem autoimmune disorders like rheumatoid arthritis, inflammation is localised primarily to the joints subsequent to the infiltration of immune cells in the synovial membrane (Liu et al., 2014). In general, this class includes Th2 (a potent autoantibody constituent) though, in organ-precise cases, autoinflammatory reactions take place against a particular organ like type 1 diabetes mellitus, which deteriorates the pancreatic cells and ultimately leads to deficiency of insulin (Katsarou et al., 2017). Likewise, autoimmune disorders of the gastrointestinal tract observed in the subsets of inflammatory bowel diseases, including Crohn's disease and ulcerative colitis (Asadzadeh-Aghdaei et al., 2019), are typically T cell–regulated processes (Bolon, 2012). A number of cases, for instance, multiple sclerosis, demonstrate both organ-specific and systemic characteristics as multiple sclerosis is distinguished by inflammation in the spinal cord and brain, resulting in myelin and axon damage, which causes disturbance in CNS (Koushki et al., 2021).

Besides T lymphocytes, numerous other immune cells including B cells are also included in emerging autoimmune disorders. Various subsets of B cells play complex roles in autoimmune illnesses (Viau & Zouali, 2005). On the contrary, cells of innate immunity such as macrophages and monocytes have been considered chief controllers of the inflammation in the liver and other body organs. Research conducted by Li et al. showed that macrophages that are M1-polarised could encourage producing HPCs (hepatic progenitor cells) with the self-restoring phenotype, which is related to stimulation of the signalling hepatic progenitor cells in PSC (primary sclerosing cholangitis) (Li et al., 2018).

Commonly Seen Autoimmune Disorders and Management with CAM Approaches

Psoriasis

Psoriasis is a chronic autoimmune inflammatory disorder that has critical genetic and immunological elements, upon which numerous factors from the environment may act to instigate the series of pathological events. In accordance with the recent data, psoriasis is affecting nearly 1 to 3% of the population all around the globe,

demonstrating the primary peak incidence between 15 and 20 years and a subsequent secondary peak between 55 and 60 years of age (Colombo, 2014). The conventional treatment approaches for psoriasis include medicine that is applied locally, including salicylic acid, analogues of vitamin D or inhibitors of calcineurin, dithranol and local or systemic corticosteroids. Moreover, phototherapy with ultraviolet B rays (UVB) is also used in the management approaches. However, complementary and alternative medicinal approaches for the management of psoriasis and alleviating the symptoms of the disease are also getting famous nowadays; these therapies include acupuncture, balneotherapy, cupping therapy, pharmacotherapy etc. There are numerous acupuncture points accessible in which disposable needles are used and inserted into certain points of skin to enhance the flow of blood and decrease the psoriatic inflammation locally; however, as of yet with an indefinite mechanism (Chen et al., 2019). A current study carried out on mice revealed that electro-acupuncture, fire needling and needling were associated with minimum local T lymphocytes and CD3+ population, as well as minimum levels of IL-1B, substance P, IL-17A, IL-23p40 and neurokinin (Wang et al., 2019) (Figure 11.1).

In accordance with Jorge et al., acupuncture of the ear has been found to be successful in managing psoriasis in around five out of seven patients, whereas another two demonstrated remarkable recovery (Jorge et al., 2016). This initiates a build-up of anti-inflammatory and antioxidant substances locally, such as bilirubin, carbon-monoxide, heme-oxygenase-1 and biliverdin, which have neuroregulatory and anti-proliferative effects (Lowe, 2017). Stress has been identified as a stimulating factor in both the exacerbation and appearance of psoriasis, exasperating the manifestation of the disorder upon the skin in over half of the patients. Psychotherapy has been researched in multiple trials and distinct case reports, with the outcomes being encouraging, even as early as thousands of years before (Schmid-Ott, 2000; Timis et al., 2021), as well as randomised controlled trials of 11 cases, which proposed that effortlessly hypnotisable cases revealed better improvements in controlling the disease (Tausk & Whitmore, 1999). Climatotherapy and balneotherapy signify already recognised methods of complementary and alternative medicine management to moderate serious psoriasis, having been validated efficiently in the instant clearing and lessening of induction across many research studies (Timis et al., 2021). A number of these studies also demonstrated a better QOL, as measured by the Dermatology Life Quality Index. Kushelevski and Harari documented a greater rate of clearance in lesions of patients with early-onset psoriasis and those with an extensive duration of the ailment (Harari et al., 2016; Kushelevsky, 1996; Timis et al., 2021).

Figure 11.1 Psoriatic skin.

Rheumatoid Arthritis

Rheumatoid arthritis is prevalent all around the globe and is impacting the lives of all ethnic groups (Jameson, 2020; Lawrence et al., 1998). Females are affected nearly three times more often than males. The age of initiation of diseases is between the later part of the 20s and the early part of the 50s; however, it can affect people of any age. Rheumatoid arthritis is a persistent disorder involving multiple systems of the body and distinguished by chronic synovitis generally involving the joints of extremities in a symmetric manner (Gorman & Cope, 2008; Jameson, 2020). The uncontrolled synovial inflammation may give rise to bone erosions, ankylosis of the joints and destruction of cartilage (Jameson, 2020). Studies conducted on families and twins specify that rheumatoid arthritis has a genetic predisposition, and nearly 70% of patients have HLA-DR1 or HLA-DR4 alleles. The utilisation of complementary and alternative medicine by patients of rheumatoid arthritis is becoming progressively famous in the United States of America and other technologically advanced countries (Venkatesha et al., 2011) (Figure 11.2).

Early utilisation of biological and allopathic DMARDs (disease-modifying anti-rheumatic drugs) has improved the outcomes of patients dramatically; though a considerable number of patients do not sufficiently react to treatment (Emery, 2012; Tarner & Müller-Ladner, 2008). In England, the prevalence of using complementary and alternative medicines for a lifetime among patients with arthritis is 38% (Ernst & Posadzki, 2011). Globally, the prevalence of using complementary and alternative medicines in patients with rheumatoid arthritis is expected to be around 20 to 86% (Tamhane et al., 2014). The most frequently utilised CAMs in rheumatoid arthritis are possibly fish oils, with 19% of cases documenting its use (Hill et al., 2009). Fish oils are drawn out either from the entire fish (mackerel, sardines and herring) or cod liver oil. They are loaded in extended chain ω-3 PUFAs (polyunsaturated fatty acids), predominantly DHA (docosahexaenoic acid) and EPA (eicosapentaenoic acid) (Wall et al., 2010). Fish oils have been demonstrated to improve the morning stiffness and the number of painful joints in patients with rheumatoid arthritis (Fortin et al., 1995) and may have an NSAID-medicines-sparing impact (Galarraga et al., 2008). In Peru, *Uncaria guianensis* and *Uncaria tomentosa* (vine species) have an extensive traditional background of use as a remedy in cases of rheumatic disorders. The active constituents are believed to be alkaloids (particularly pentacyclic oxindole); however, they also consist of other antioxidants. Extracts

Figure 11.2 Depiction of rheumatoid arthritis in hand.

have immune-stimulatory activities in vitro and a number of benefits in rheumatoid arthritis when utilised with other disease-modifying anti-rheumatic medicines (Mur et al., 2002). Another medicine, rose-hip, is produced from the shells, fruits and seeds of a species of *Rosa canina* and is reportedly loaded with antioxidants (Halvorsen et al., 2002), such as vitamin C and polyphenols, and also a galactolipid identical to GLA (Larsen et al., 2003; Willich et al., 2010). *Rosa canina* has been demonstrated to make the measures of illness activity better (Willich et al., 2010) while adverse effects are mild and unusual (Christensen et al., 2008; Winther et al., 2005). *Zingiber officinalis* is one of the most commonly used herbs all around the globe and is claimed to have anti-inflammatory and antioxidant activities. In traditional Chinese medicine, ginger has been utilised for millennia to manage inflammatory disorders (Altman & Marcussen, 2001). Furthermore, vitamin D is significant for calcium metabolism, which is significant in rheumatoid arthritis as it is related to fractures, falls and osteoporosis (Lems & Dijkmans, 1998). Numerous studies have revealed lower levels of vitamin B6 in rheumatoid arthritis contrasted with controls who have good health, and levels have also been related to enhanced production of cytokines, such as TNF (Huang et al., 2010; Roubenoff et al., 1995). Impaired status of vitamin B6 could be an outcome of inflammation, and these cases may have greater vitamin B6 demand. High dose experiments of vitamin B6 have documented improvements in profiles of inflammation but not the inactivity of disorder; there are several other complementary and alternative medicinal approaches utilised by the patients of rheumatoid arthritis, principally to decrease pain, including techniques of mind and body (Cramp et al., 2013), electrical stimulation (Brosseau et al., 2002), electro-acupuncture and acupuncture (Casimiro et al., 2005), massage therapy (Gok Metin & Ozdemir, 2016) and laser therapy (Brosseau et al., 2005). Another significant non-medicinal complementary and alternative medicinal approach with association to conventional therapy for rheumatoid arthritis is making modifications in diet. In general, regimes include the Mediterranean, fasting and vegetarian kinds of diets (Hagen et al., 2009).

Inflammatory Bowel Disease

IBD (inflammatory bowel disease), consisting of ulcerative colitis and Crohn's disease, is a common autoimmune disorder that can be responsible for causing abdominal pain, blood in stool and diarrhoea (Mowat et al., 2011). Inflammatory bowel disease is distinguished by its activity period, inactivity and relapse (Liverani et al., 2016). Research reports nowadays propose that nearly half of all patients with inflammatory bowel disease consume some kind of complementary and alternative medicine to assist in the treatment of their ailment and its associated symptoms (Picardo et al., 2020). Among the most reported remedies, curcumin emerges to have a spectrum of medicinal properties and has been traditionally utilised in a range of inflammatory disorders (Gupta et al., 2013). In the last 20 years, curcumin was established to be the active constituent of turmeric and has anti-inflammatory activities. There is compelling research to assess its benefits in numerous medicinal fields (Aggarwal & Harikumar, 2009). Curcumin works by subduing several cytokines, specifically NFκB, IL-2, TNF-α and interleukin-1, in addition to downregulating Janus kinase and the ICAM-1 (intracellular adhesion molecules-1) (Picardo et al., 2020). There has been enhanced interest in the utilisation of ω-3 fatty acids

because of their immunostimulatory and anti-inflammatory effects (Simopoulos, 2002). Verifications from models of murine have revealed an association with ω-3 levels and regulation of pro-inflammatory moderators (Peterson et al., 1998; Yaqoob & Calder, 1995). A number of human studies have also demonstrated that enhanced intake of ω-3 fatty acids decreases the synthesis of the leukotrienes, prostaglandins and thromboxanes (inflammatory mediators of eicosanoid), giving rise to a shift to an anti-inflammatory characterisation (Marion-Letellier et al., 2015; Simopoulos, 2002). Probiotics have been utilised for several conditions of health, with increasing pieces of evidence about their strong benefits in the gut, including inflammatory bowel disease (Picardo et al., 2020). Probiotics were established to be the most frequently used supplements (nearly 64%) among the users of complementary and alternative medicines that visited a clinic of gastroenterologists (Hung et al., 2015). Furthermore, aloe vera is among the most commonly used natural product by patients with inflammatory bowel disease. It has been documented to have immunomodulatory as well as anti-ulcer activities (Pugh et al., 2001; Suvitayavat et al., 2004) (Figure 11.3).

Nowadays, an alteration of the gut microbiota is contemplated to be a significant factor in the development of inflammatory bowel disease, and this alteration provides a promising pathway for nutritional controls of the microbiome that may inhibit inflammation in these conditions (Aroniadis & Brandt, 2013). Diet has been revealed to regulate the intestinal flora's stability; hence, it is presumable that altering the diet can have an impact on the inflammatory reaction (Paturi et al., 2012). The specific carbohydrate diet was made famous for the treatment of IBD by the book *Breaking the Vicious Cycle* by Elaine Gottschall (a biochemist) following her daughter's management of ulcerative colitis by this diet (Gottschall & Gottschall, 2020). The specific carbohydrate diet is developed on the theory that polysaccharides and

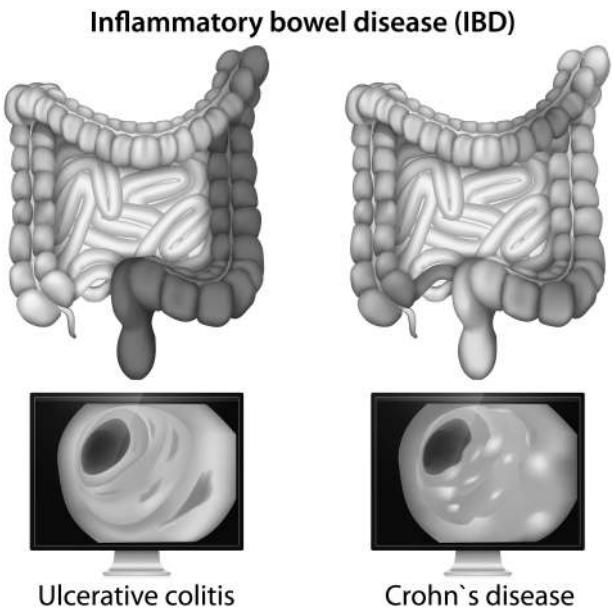

Figure 11.3 The intestinal regions affected by inflammatory bowel disease.

disaccharides eliminate from the body without getting absorbed into the colon, resulting in an overgrowth of fungus and microbes, which ultimately causes excessive mucus synthesis. The specific diet of carbohydrates permits the consumption of only monosaccharides. Another type of diet is the paleo diet, which was popularised by Dr Walter L. Voegtlin, a famous gastroenterologist who wrote a book on it called *Stone Age Diet* (Voegtlin, 1975). The notion behind this diet is that the gastrointestinal tract of humans has not been made to operate and hold the modern diet, which is enriched with agriculturally acquired foodstuffs. The Stone Age diet focuses on the intake of non-cereal, lean, non-tamed flesh of animals and plant-based diets. The Stone Age diet favours the concept that lean protein should be the resource of 30 to 35% of daily caloric consumption and an extreme-fibre diet from non-cereal, botanical-based sources, up to 45 to 100 grams every day (Eaton & Konner, 1985).

Systemic Lupus Erythematosus

SLE is an autoimmune disorder distinguished by inflammation in all systems. Patients of systemic lupus erythematosus unpredictably and alternatingly experience sudden progression or spread of disease in which the immune system can attack any system of the body. Systemic lupus erythematosus is related to greater than normal proportions of CVD (Manzi et al., 1997), which is one of the most frequent reasons for mortality (Ward, 1999). Regularly, many SLE patients experience considerable pain and fatigue, and several others are incapable of executing any task because of the disease (SLE). Anxiety and depression are prevalent, influencing up to 65% of cases (Bachen et al., 2009). Some of the most encouraging developments in complementary and alternative medicinal approaches for systemic lupus erythematosus are vitamins and supplements. In accordance with the epidemiological research, decreased consumption of antioxidants, vitamin C and vitamin D in adolescence is not an etiological factor for the development of rheumatoid arthritis or systemic lupus erythematosus in later ages. However, there are several verifications that these supplements, along with other supplements, may make the SLE symptoms better and decrease the risk of common comorbidities of SLE. Vitamin D greatly impacts bones, immune systems and cardiovascular systems (Greco et al., 2013). Vitamin D deficiency is prevalent in the overall population and even more frequent in patients with systemic lupus erythematosus (Kamen, 2010; Kamen & Aranow, 2008). In one of the cohort studies of 177 patients of SLE in Hungary, low levels of vitamin D was established in around 82% and was related to the activity index of SLE disorder and intensity of serological indicators like dsDNA (Szodoray et al., 2011). In Japan, potential observational research followed around 241 adult females with dormant systemic lupus erythematous over four years and established that consumption of vitamin C by means of food was inversely related to the risk of acquiring active disorder (Minami et al., 2003). CVD is a leading cause of death in patients with systemic lupus erythematosus (Ward, 2000). The subclinical vascular disorder is more frequent in systemic lupus erythematous than in general people (Manzi et al., 1997). Hence, supplements like ω-3 PUFAs that have vascular and cardio-protective effects in the general population (Bucher et al., 2002) along with anti-inflammatory effects (James et al., 2000) may also be beneficial for people with systemic lupus erythematosus (Figure 11.4).

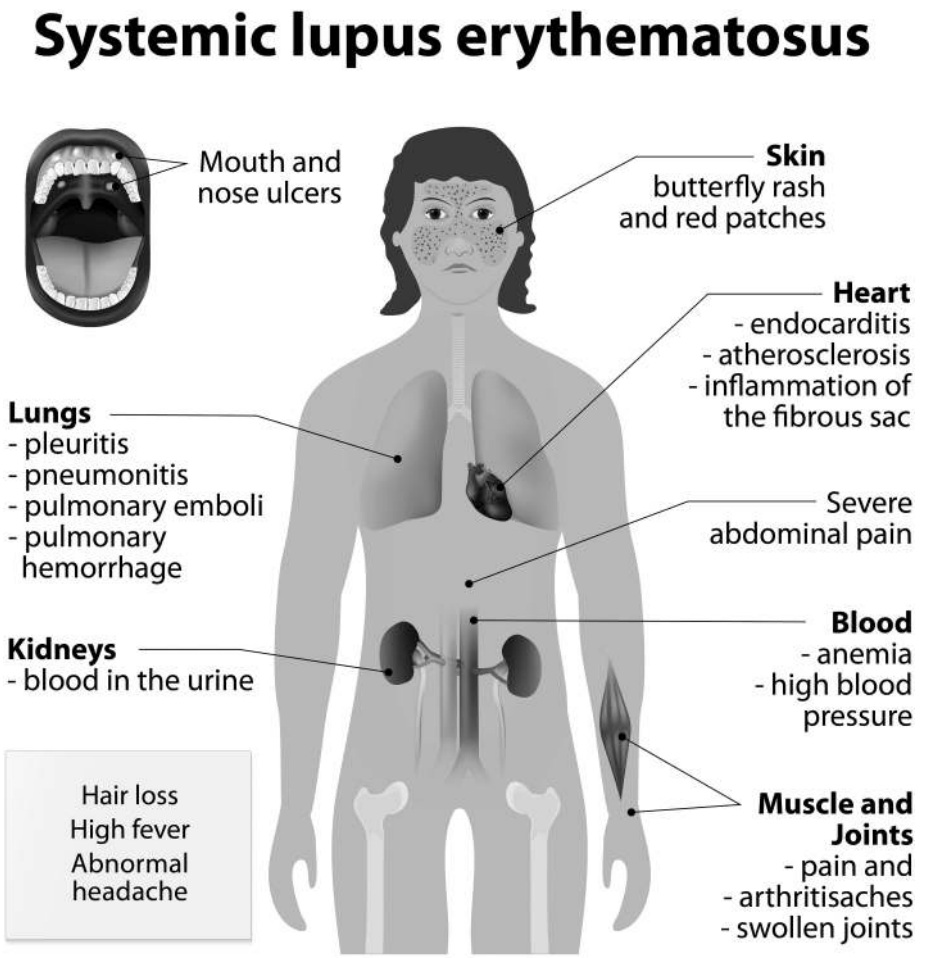

Figure 11.4 Symptoms of systemic lupus erythematosus.

Turmeric can suppress tumour progression, development of inflammatory bowel disease and synthesis of inflammatory cytokines; furthermore, curcumin can decrease cholesterol and improve the healing of wounds. According to a case study of a patient with lupus nephritis that combined 1.8 grams of N-acetyl cysteine per day with therapy for the management of systemic lupus erythematosus led to decreased fatigue, improved proteinuria and decreased activity of disease (Tewthanom et al., 2010). Diminished quality of life, pain, functional restrictions and fatigue are commonly seen in patients with lupus. Psychiatric disorders have impacted up to 65% of patients with SLE over the course of their lives (Bachen et al., 2009), and the frequency of psychiatric diseases in systemic lupus erythematosus is more significant than in other prolonged, inflammatory autoimmune disorders such as ankylosing spondylitis and rheumatoid arthritis (Sundquist et al., 2008). It's critical to address the mood disorders and quality of life, as depression has been associated with drug non-adherence as well as an increased risk of cardiovascular diseases in patients

with SLE. Mind-body therapies for systemic lupus erythematosus may include training in problem-solving, meditation, physiological relaxation and positive communication methods, as well as identifying and changing distorted or problematic thinking processes (Greco et al., 2013).

Multiple Sclerosis (MS)

MS is a persistent incapacitating disorder of the central nervous system that impacts the lives of around 500,000 individuals in the United States of America. Pathogenesis of MS is thought to include an autoimmune reaction within the central nervous system, ensuing in multifocal demyelination with a range of injuries to axons (Noseworthy et al., 2000). Demyelination and inflammation appear to be the primary cause of disease development in the deteriorating forms of multiple sclerosis, while neurodegeneration, being the source of degeneration for axons, appears to influence the pathology in intensifying forms of the disorders (Bjartmar et al., 2003).

There has been a range of research studies documenting the frequency of CAM applications by patients with multiple sclerosis, and the variety of prevalence is absolutely wide, at around 33 to 70%. A number of patients with multiple sclerosis utilised complementary and alternative medicinal approaches and documented benefits from the frequently utilised treatment modalities, which include antioxidants and ω-3 fatty acids. Moreover, to the recognised benefit, the causes of using complementary and alternative medicinal approaches include the wish to improve general health, alleviate psychological and physical symptoms, and inculcate holistic health approaches. Extracts of *Ginkgo biloba* have a range of pharmacological activities that suggest they may increase cognitive performance and change neural functions. Cognitive disablement can be a significant cause of disability and morbidity and can have an impact on around 40 to 50% of patients with multiple sclerosis. *Ginkgo biloba* has been advised to make cognitive performance better in Alzheimer's disease, as observed in clinical experiments and a number of other research (Yadav et al., 2010) (Figure 11.5).

In one of the research surveys conducted of 1,980 patients with multiple sclerosis, around 30% replied that they had taken part in yoga classes. Among these people, 57% stated that they had established yoga to be 'quite beneficial'. In research among 150 cases with secondary-developing or relapsing-remitting multiple sclerosis, participants assigned randomly to around two months of general care programme or mindfulness training outcomes demonstrated inhibition of fatigue, anxiety and depression along with improvements in quality of life after intervention and at follow-up of around six months in the training strategy. Nearly two-thirds of patients surveyed documented the application of acupuncture for managing multiple sclerosis. The symptoms reported to decrease in a number of acupuncture studies specific to multiple sclerosis were numbness, dysfunction of bowel and bladder, pain, spasticity, fatigue, muscle stiffness, problems with coordination, insomnia, depression and trouble walking. Dysfunctioning of the bladder was documented to diminish after both electro-acupuncture and standard acupuncture (Horowitz, 2011). In the UK a study was conducted regarding the usage of complementary and alternative medicine by people with multiple sclerosis; chiropractic (42%) was the third most common treatment modality documented after massage (44%) and physiotherapy (52%)

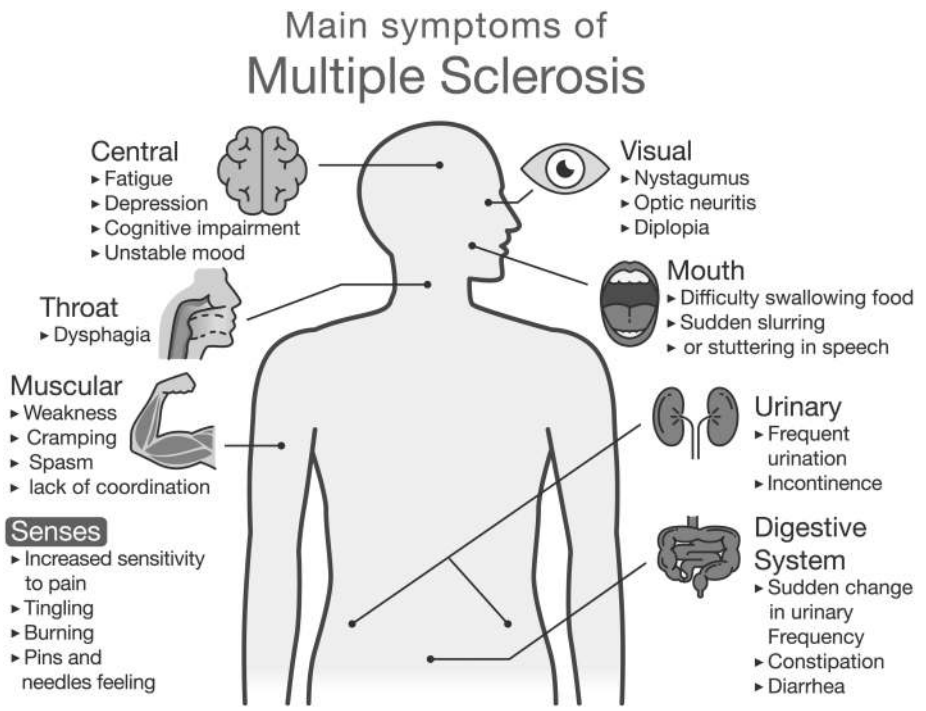

Figure 11.5 Symptoms of multiple sclerosis.

(Carson et al., 2009). Moreover, magnetic field therapy has been demonstrated to be helpful in fatigue, a symptom impacting ~75% of cases (Piatkowski et al., 2009).

Multidimensional Approach towards Cancer

Cancer has afflicted animals and humans throughout documented history. It's not astonishing, then, that humans have written regarding cancer from the earliest times. Human mummies in ancient Egypt, fossilised tumours of bones and old writings contain some of the earliest indications of cancer. Mummies have been found with growths that resemble osteosarcoma, a type of bone cancer. The Greek physician, Hippocrates, also recognised as the 'Father of Medicine', is attributed with coining the terms *carcinoma* and *carcinos*. Hippocrates utilised the words for non-ulcer-causing and ulcer-causing tumours. These Greek terms relate to a crab, and they were most probably assigned to the disease because cancer's finger-like spreading extensions resembled the appearance of a crab. Celsus, a Roman doctor, later interpreted the Greek phrase into *cancer* (Latin name for crab). Another Greek physician, Galen, used the term *oncos* (Greek word used for swelling) to represent tumours. Cancer was blamed on the gods by the ancient Egyptians, while Hippocrates' theory about cancer is that there are four humours in the human body, blood, phlegm, yellow bile and black bile; the person is considered healthy if all four body humours are in equilibrium. Either excess or insufficiency of any of the body humours was believed to give rise to sickness. Cancer was supposed to be caused

by an abundance of black bile in various body regions. The Romans carried this notion of cancer supported by the renowned doctor Galen's teaching of medicine, which went unquestioned for almost 1,300 years into the Middle Ages (American Cancer Society, 2014). In Ayurveda, cancer is represented as a non-inflammatory or inflammatory growth in the *Charaka* (Agnivesa et al., 1976) and *Sushruta* (Susruta & Kunja Lal, 2006) *Samhitas* and is referred to as either major neoplasm (*arbuda*) or small neoplasm (*granthi*). *Kapha* or water (the arterial system), *vata* or air (nerve system) and the *pitta* or fire (venous system) are defined in Ayurvedic texts as three controlling systems of the body that work together to conduct the body's normal functions. While one or two of the three biological systems are out of balance in benign neoplasia (*kaphaja*, *vataja* or *pittaja*), it is not too detrimental since the body is still striving to harmonise these systems. On the other hand, malignant tumours or cancers (*tridosaja*) are extremely dangerous since all three key physiological systems lose reciprocal synchronisation and so are unable to prevent tissue destruction, culminating in a fatal pathological state (Susruta & Kunja Lal, 2006).

According to the *Sushruta*, pathogens that negatively influence all body regions are the primary cause of big neoplasms. These aberrant growths' non-communicable and non-suppurative characteristics have been attributed to extra fat or water in the tumour corpus and the rigidity and strict containment of the *doshas* (body humours) in a specific location (Balachandran & Govindarajan, 2005). The *tridoshas* are used to explain pathophysiology in Ayurveda; digestive and metabolic functions of the human body are controlled by *agni* or *pitta*, which is found in every cell. In *arbuda* (major neoplasm), the diminished state of deranged metabolism (*dhatwagni*) gives rise to excessive growth of tissues because the drop in *agni* (fire) is inversely proportional to the associated tissue. The anabolic growth stage is linked with *vata*, while the catabolic (destructive) phase is associated with *kapha*. Cancer develops due to a metabolic crisis, in which *vata* forces are increased, and *kapha* forces are suppressed, resulting in cell multiplication.

Any realistic method to tackle this awful disease is vital. The use of therapeutic plant-based medicines to halt the disease's insidious character is a substitute for western management, which has serious adverse effects. Numerous herbs have been researched in clinical trials and are constantly being explored phytochemically to learn more about their tumour-inhibiting impact on different malignancies. As a result, the patients with cancer who have already been afflicted by the disease and are now suffering from drug-induced hazardous adverse effects are turning to CAM in the hopes of finding a better solution. The medicinal approach of Ayurveda has been distributed into four classes: spiritual method (*Naishthiki chikitsa*), management of disease (*Roganashani chikitsa*), maintenance of health (*Prakritisthapani*) and restoration of regular functions of the body (*Rasayana chikitsa*) (Balachandran & Govindarajan, 2005) The upcoming era may be called as an era of medicine with 'multidimensional approaches'. This will go further from the recent integrative methods to extensive and profound practice and perspective, which entirely honours every element of 'as human beings who we are' whether practitioners of CAM, family members, nurses, technicians, patients, doctors or society as an entire unit. The initial chief element is that human beings should finally and without any embarrassment recognise that all of them are multidimensional creatures. At the most fundamental level, this means that every human being has a heart, soul and mind along with a physical body—not to mention significant and profound interpersonal associations—and that the job of humans is to care and honour for all these dimensions with equivalent integrity and

skill. A multifaceted care approach will entail a more clearly articulated mission, vision and agreement on what we're here to accomplish and be for cancer patients and their families and our coworkers, communities, members of our own family and ourselves. Proactively considering the multidimensional wants and issues with people will deliver a deeper, more thorough and more gratifying experience for everyone engaged.

CAM approaches are also utilised among patients of cancer; however, the percentage varies depending on the type of cancer and other circumstances. Davis et al. (2012) reviewed studies demonstrating CAM use ranging from 11 to 95% among cancer patients; however, many studies suggest one-third to one-half (Knecht et al., 2020). Diet plays a significant role in the aetiology and prevention of cancer. Various organisations have developed scientifically proven dietary guidelines for reducing the risk of cancer development, suggesting people should decrease intake of fat, especially from animal sources, enhance intake of fibre, include a wide range of fruits and vegetables in their regular diet, be healthy and active physically by maintaining a healthy weight, take alcohol in moderate amounts, if at all, and limit salt-pickled, salt-processed or food that is smoked. Considerable evidence for inverse risk relationships with intake of fruits and vegetables subsists for carcinoma of the rectum, lung, pharynx, stomach, mouth, colon and oesophagus (Glade, 1999; Greenwald et al., 2001). Verifications from different epidemiological studies propose that risk of breast and colorectal carcinoma may be diminished by enhancing the consumption of food that is loaded with fibre including fruits, whole grains, cereals and vegetables (Greenwald et al., 2001). Wheat bran loaded with dietary fibre along with different vitamins and plant chemicals is related to a decreased risk for breast and colon carcinomas (Ferguson & Harris, 1999; Reddy, 1999). Generally, the foods consumed, especially fruits and vegetables, are sources of several micronutrients. A number of these include vitamin E, β-carotene, selenium and vitamin C, all of which have an antioxidant perspective along with vitamin D, folate and calcium, which have been the centre of attention for considerable epidemiological and experimental research to identify their impact on the risk of cancer (Choi & Mason, 2000; Greenwald et al., 2001; Heber, 2006; International Agency for Research on Cancer, 1998; van Poppel & van den Berg, 1997). Literature from epidemiological studies that associated either enhanced consumption of β-carotene-loaded fruits and vegetables or increased concentrations of β-carotene in blood with risk of developing cancer have found constant evidence of a considerable inverse relationship with risk of lung carcinoma (Cooper et al., 1999; Glade, 1999; Ziegler et al., 1996). At the same time, the studies regarding diets rich in vitamins consisting of fruits and vegetables stipulate that probably vitamin C reduces the risk of gastric carcinoma and perhaps diminishes the risks of developing carcinomas of the cervix, oesophagus, mouth, lung, pharynx and pancreas (Glade, 1999). Data from the trial of the general population in Linxian specified a remarkable relationship between levels of selenium in serum and a decreased risk of gastric and oesophagal carcinomas. The researchers analysed that around 26.4% of these carcinomas in Linxian are regarded as being caused by low levels of selenium (Mark et al., 2000). Research trials in a range of animals have revealed that selenium can decrease cancer development (Heber, 2006).

According to experimental and epidemiological evidence, calcium and vitamin D may impact the risk of colorectal and prostate carcinomas. Allium vegetables have high quantities of organosulphur constituents and have an inverse relationship with cancer; according to epidemiological studies (Glade, 1999; Heber, 2006); allium vegetables were found to have an inverse association with the overall risk of cancer

development in 27 out of 35 cohorts and case-control studies, and an inverse association with gastric carcinoma in nine out of 11 case-control studies (Glade, 1999). One analysis of around 72 research studies about tomatoes (rich in lycopene) and products made up of tomatoes and cancer established the most powerful association with gastric carcinomas (Giovannucci, 1999). Lycopene has currently been demonstrated to decrease the activity of IGF-1 in cancer cells of the breast (Karas et al., 2000). Results from the epidemiological research studies that analysed the consumption of black and green tea on cancer risk propose that intake of green tea may decrease the overall fatality risk of cancer (Kuroda & Hara, 1999). The laboratory and epidemiological data advise that dietary plant estrogens—that is, lignans and isoflavonoids—inhibit the risk of particular cancers. Products made up of soy have been related to a diminished risk for prostate, breast and endometrial carcinomas (Greenwald et al., 2001). Oil extracted from the olive plant is loaded in oleic acid, a MUFA (monounsaturated fatty acid), and also consists of several antioxidants that may have the potential for decreasing the development of cancer (Owen et al., 2000). Several epidemiological studies have estimated the roles of anthropometric measures such as weight gain, BMI (body mass index) and central obesity in association with the risk of cancer (Glade, 1999; Heber, 2006).

With anthropometric measurements, the strongest findings suggest a link between kidney, endometrium, breast and colon cancers. For example, numerous studies show that women in the greatest weight quintile had a twofold or threefold risk of developing endometrial carcinoma. Many studies regarding physical workouts, including recreational and occupational activity, show that physically active women have a lower risk of breast cancer, though dose-response trends are rarely seen (Greenwald et al., 2001).

Conclusion

CAM therapies and natural products tend to subdue inflammation and control autoimmunity by changing particular molecular pathways. For instance, the anti-inflammatory activities of numerous constituents such as polyphenols extracted from different plants have been ascribed to show antioxidant activities. Researchers have established that various nutritional supplements, herbal products, psychological therapies, diet therapy and other CAM approaches greatly impact different immunity parameters. However, detailed studies and extensive randomised, controlled trials are necessary to prove the significance of these therapies and to understand the pathological, biochemical, immunological and molecular aspects of diseases. Moreover, the stress-reducing techniques should also be assessed by conducting extensive experiments to identify how stress aggravates autoimmune disorders and cancer and how to overcome stress.

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Part 2

TRADITIONAL PHARMACOTHERAPY AND IMMUNITY

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Chapter 12

Common Medicines from Herbs, Minerals and Animal Sources

Introduction

Plant, mineral and animal products have been in use for many decades and are considered a substantial source of food and medicines. Humankind has always depended upon nature and its remedies to alleviate their physical or mental symptoms. The most primitive humans on Earth have utilised these nature-based remedies and attempted uncomplicated and fundamental surgical procedures (Iqbal, 2022). Pharmaceuticals and drugs have become essential; they have performed considerable roles in managing and preventing various ailments since the outcome is a better life expectancy. Hence, people started assuming that drugs could provide wellness and health. Nowadays, numerous drugs are falling short because of toxic or unexpected outcomes, and the arduous search for safer and better drugs carries on even more dynamically. The Oxford English dictionary describes a drug as 'any matter which possesses a physiological impact when consumed or otherwise administered into the body'. Contrarily, the word medicine is described as 'a drug or any composition for the prevention or for disease management'. In consequence, the word drug is generally applied to indicate a matter that may have toxic or medicinal properties (Patwardhan & Vaidya, 2010).

The historical usage of drugs in several forms to alleviate symptoms and manage diseases dates back to prehistoric times and consists of several absurd remedies. The determined pioneering attempts to systematically classify several mineral, botanical and animal sources are accessible in ancient Chinese, ancient Ayurveda, Greco-Arabic and Tibetan texts. These old pieces of literature also give details about which plant parts (seeds, stem, gum, flowers, roots, resin, bark, leaves) must be utilised to manage clinical indications; whether individually or in blend with other substances; moreover, in what dosage form they should be used (linctus, syrup, tablets, liquids); along with their processing methods (Patwardhan, 2000).

Organic products, such as fungal, botanical, shell, mineral, bee and animal products, constitute the earliest medical management form. Currently, several typically

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consumed drugs originate from herbs. Around 25% of the recommended drugs consist of at least one herbally originated active substance or synthetic constituent, which resembles a plant-extracted compound. More than 80,000 herbs are being used for their therapeutic uses throughout the globe. Typically, a particular plant part is utilised for medicinal preparations such as creams, extracts, tablets, tinctures, infusions or ointments. The therapeutic activities of such medicines are frequently reported under the categories of very common terminologies, such as laxative (a substance that is used to enhance the movements of the bowel and alleviate constipation), carminative (a substance that prevents the collection of gas in the GI tract or assists in the elimination of gases), antiseptic (to decrease the probability of infection), antitussive (an agent that inhibits cough) or demulcent (a substance that creates a smooth film on top of a mucous membrane, alleviating inflammation and minor pain) (Saad & Said, 2011).

Contrary to synthetic medicines, which typically comprise only one and usually an unnatural or man-made chemical, plant-based or natural medicines comprise numerous compounds. Natural medicines are categorised in lots of European regions as drugs, and in the United States of America, they are sold as nutritional supplements. Safety evaluation of natural products has frequently been disregarded because long-established and seemingly safe consumption is typically considered apparent. This is not astonishing because the products made up of herbal ingredients are compound blends of secondary metabolites, a number of which are potentially poisonous (e.g. nephrotoxic and hepatotoxic) plants, and their products with therapeutic effects have traditionally been consumed all around the world for prevention and management of most identified forms of ailments. A basic and clinical scientific study proved the mechanism of action and efficacy of various plants for managing different diseases, including hypertension, diabetes, hepatic and dermatological disorders. Nowadays, lots of advised medicines are derived from herbs, such as silymarin (*Silybum marianum*) which has been demonstrated to have clinical uses in the management of hepatic disorders, including viral hepatitis, cirrhosis, fatty liver disease (FLD), radiation toxicity, toxic hepatitis and ischaemic injury by means of its anti-inflammatory, antifibrotic, antioxidative and antilipid peroxidative activities. Moreover, silymarin has revealed hepatic regenerating and immunomodulating effects. One more example is *Nigella sativa*; the seeds of the black seed plant are recognised to have lots of therapeutic activities and are extensively consumed in Greco-Arabic and Islamic medicine. The toxicological properties and management potential of the black seed plant have been studied considerably. A search of MEDLINE utilising 'black seed' or '*Nigella sativa*' shows over 700 citations, including anti-inflammatory, antifertility, antidiabetic, antinociceptive, immunomodulatory, antioxidant, hypotensive, uricosuric, anticancer, antihistaminic and choleretic effects (Fugh-Berman, 2000; Pak et al., 2004; Rousseaux & Schachter, 2003; Saad et al., 2005, 2008; Watson & Preedy, 2011). Since the beneficial and toxic effects of the full range of natural products can't be covered in this chapter, though, this chapter will highlight the importance of some commonly used herbs, minerals and animal products in their preparations and what the indications are for using those medicines.

Traditional and Modern Usage of Natural Products

Paleopathological research studies show that health disorders have continued to exist for thousands of years. Archaeologists have discovered the skeleton of a human in a cave that dates back 60,000 years in the northern parts of Iraq. The skeleton demonstrates degenerative bone disorders, managed fractures and numerous damaging

injuries. In Mesopotamia, another skeleton was established to date as early as 5000 BC. As the Sumerians are ascribed to be the earliest civilisation of humans, it is not astonishing that in Mesopotamia, excavations demonstrate the presence of a Sumerian medical practitioner's seal as early as 3000 BC, which is one of the earliest pieces of evidence of the physician's presence. In addition to the discovery of writing and the wheel, the Sumerians are also attributed with the invention of early cosmetics, barley beer brewing and drugs. Moreover, it is not astonishing that the historical Mesopotamians comprehended that a number of diseases are infectious. They probably had an encounter with crucial infectious disorders such as the plague or slight illnesses such as a cold. Identical development was found in Egypt as medicine of Egyptians dates back to around 2900 BC; however, the best-identified record of Egyptian pharmaceuticals is the Ebers papyrus from 1500 BC. The Ebers papyrus reported around 700 animal- and herb-based medicines and consists of formulations such as honey, gargles, poultices, wine, ointments, beer, snuffs, infusions, milk and pills being frequently utilised as vehicles (Patwardhan et al., 2015b).

Galen (129–200 AD), the Greek physician, invented the foremost modern pharmacopoeia, explaining the uses, appearance and properties of several botanicals of his era. The basis of the contemporary pharmaceutical field was laid when methods to manufacture synthetic substitutes for a multitude of organic medicines were discovered. The chemistry of natural products, as a branch, appears to have started in 1804, when Friedrich Serturner, a German pharmacist, separated morphine from *Papaver somniferum*. He was the earliest chemist to segregate an alkaloid from a plant. Morphine was acquired from the poppy plant, properties of which were identified for more than 5,000 years.

While the seeds of synthetic medicines were planted in 1874 when salicylic acid was separated from the plant of *Salix alba* (willow bark), which is the forerunner of the synthetic medicine commonly identified as aspirin, research in the pharmaceutical industry took a considerable forward leap when synthetic organic chemistry was discovered. Throughout that duration, biochemists, microbiologists and pharmacologists started to unearth the chemistry of natural humans, microorganisms, animals and plant processes. This gave rise to the recognition of several chief chemical molecules and bestowed more chances to discover new constituents. Lots of new compounds appeared to manage cancers, infections, ulcers, infestations and conditions of blood pressure and heart. A range of drugs was discovered by means of screening a huge number of synthetic chemicals. Several also appear accidentally, found as an outcome of the sharp-sighted scientist's and physician's observations. Examples of such compounds include penicillin, isoniazid, antihistamines, sulfonamides and antipsychotic drugs. Nowadays, scientists in the field of pharmaceuticals are encountering problems in discovering novel lead molecules, scaffolds and templates in the limited world of chemical variation. Many unnatural medicines have negative and intolerable adverse effects. There have been spectacular successes with plant medicines, most peculiarly, artemisinin or *qinghaosu* from Chinese medicine.

Substantial research on clinical therapeutics, pharmacognosy, pharmacology and chemistry has been executed on medicinal plants. A range of molecules have emerged from the experiential bases of traditional medicine, such as phyllanthins as antivirals, guggulsterone as a lipid-reducing agent, *Rauwolfia* alkaloids for managing hypertension, *Mucuna pruriens* for Parkinson's disease, picrosides for liver protection, curcumin for inflammation, psoralens for vitiligo, *Holarrhena* alkaloids for amoebiasis, piperidines as enhancers of bioavailability, withanolides and several other glycosides and steroidal lactones as immunomodulators and bacosides for the storage and

maintenance of memory (Patwardhan, 2000). The extensive plant screening for identifying novel leads from the drugs is inefficient and extremely expensive. There is proof that knowledge of traditional medicine can provide lead molecules for the management of cancer and acquired immunodeficiency virus (Cragg et al., 2007). It is approximated that more than 100 novel leads from nature-based products are in the stage of clinical development (Harvey, 2008). Around 75% of anti-infective and 60% of anticancer medicines approved between 1981 and 2002 are derived from natural products (Gupta et al., 2005). Several experts believe that it would be more efficient and cost-effective to research the plants discussed in ancient medicinal texts (Holland, 1994).

A range of active constituents from the sources of traditional medicine could act as good scaffolds and emerging compounds for logical drug design. Lots of these constituents are part of regularly consumed, traditional medicines, and thus, their safety and tolerance are comparatively better identified than any other chemical substances that are novel for human consumption (Patwardhan et al., 2008). A range of ancient pieces of literature, including the Ebers papyrus, *Sushruta Samhita*, *Charaka Samhita*, Avicenna's *Canon of Medicine* and the *Neijing Suwen* (*Yellow Emperor's Classic of Medicine*), consist of comprehensive descriptions of hundreds of medicinal plants and thousands of formulations as traditional medicinal systems dealing with the sustenance and protection of health, healthy lifestyle, prevention, diagnosis and management of the disease since all the traditional medicinal systems depend upon the utilisation of time-tested remedies for the management of common diseases.

One of its examples includes alkaloid reserpine, separated from Indian snakeroot, also recognised as *Rauwolfia serpentina*, which was a significant invention made by utilising the approach of reverse pharmacology. In 1931, the Indian chemists persuasively showed the tranquillising and antihypertensive activities of the plant. They also noticed distinctive adverse effects, such as gynaecomastia, depression, extrapyramidal syndrome and a number of adverse effects (Patwardhan et al., 2015a). In 1949, Rustom Jal Vakil, who evolved cardiology in India, conducted a trial of Indian snakeroot on subjects with primary hypertension, which documented a drop in diastolic and systolic blood pressure (Vakil, 1949). It took many years to describe the mechanisms of these adverse effects. This determined attempt gave rise to a turning point for new drugs such as prolactin-inhibiting agents, antidepressants and medicines for Parkinson's disease (Svensson, 1980). One more example of reverse pharmacology is a medicine prepared from the seeds of *Mucuna pruriens* for the management of Parkinson's disease (Manyam et al., 2004; Vaidya et al., 1978).

The admiration of Kampo, Islamic medicine, Ayurveda, Greco-Arabic and traditional Chinese medicine has enhanced globally over the past 20 years, possibly invigorated by the faith that these systems thrived for centuries due to their structural strengths and since they primarily emphasise organic product-based blends. Other components adding to the perception that natural remedies are safe to use are the rapid surge in cost of prescribed medicines, limited access to doctors imposed by treated care and reports from media regarding the side effects of advised medicines. In 2008, approximately 4.8 billion dollars were expended in the US on herbs and other plant remedies. In Europe, Germany is the dominant country followed by France for the consumption of natural drugs.

Nearly 80% of medical practitioners in Germany advise herbs, such as St John's wort, which is frequently prescribed for depression. Likewise, ginkgo is undergoing large-volume sales in Europe. Historical proofs demonstrate that the study of natural products dates back to more than 4,000 years ago in Mesopotamia. The documents from Babylonian king Hammurabi consist of instructions for utilising

medicinal herbs. Hammurabi suggested the consumption of *Mentha piperita* for indigestion or other digestion issues.

Furthermore, Sumerians utilised *Papaver somniferum*, *Cedrus* species, *Glycyrrhiza glabra*, thyme, *Cupressus*, *Sempervirens* and *Commiphora* species, all of which are still consumed by people in recent times for the management of ailments varying from cold and coughs to inflammation and parasitic infestations. Ayurveda has used several herbal medicines such as turmeric probably as early as 1900 BC. In contrast, Egyptian medicine dates back to around 2900 BC. Acharya Charaka and Sushruta later discussed numerous minerals and herbs consumed in Ayurveda. The *Sushruta Samhita*, ascribed to Acharya Sushruta, inscribed in the sixth century BC, discusses around 700 therapeutic plants, 57 animal-based preparations and 64 mineral preparations. The content of Chinese medicine has been widely reported over hundreds of years, with the foremost record dating from around 1100 BC (*Wu Shi Er Bing Fang*, consisting of 52 formulations), followed by pieces of works like the Tang herbal (850 medicines) and the Shennong herbal (365 medicines). Before the 17th century, the understanding of natural medicine was spread widely all around Europe.

Nicholas Culpeper, an English herbal physician, wrote one of the esteemed pharmacopoeias of herbal medicine that the ordinary person can consider for maintaining health. It is still extensively quoted and referred to nowadays. Culpeper always wanted to be a remarkable physician. In contrast, he preferred training from a skilled apothecary and ultimately started his store. He served the underprivileged persons in London and got identified as their community physician. The natural medicine he manufactured was intended for the common man. The foremost pharmacopoeia of the USA was published in 1820 and got legal status for therapeutic preparations in 1906. It consisted of a reliable listing of natural medicines, discussing their dosage, properties, purity, experiments and medicinal uses (Saad & Said, 2011).

Common Herbs Used as Medicine

Nature-based products have a wide variety of multifaceted chemical compounds; simultaneously, the use of natural products as modifiers of biological function has also acquired significant attention. Afterwards, they have been used successfully in the discovery of novel drugs that had an extensive influence on biological chemistry (Butler, 2008; Hong, 2011; Rosén et al., 2009). As a successful instance of the development of medicine from natural products, artemisinin and its derivatives have been extensively used in the recent era for the management of malaria. This reveals how natural product research has created a substantial contribution to the development of drugs (Cragg & Newman, 2013; Muschietti et al., 2013). Among anticarcinogenic medicines approved in the time range of around 1940 to 2002, nearly 54% were nature-originated drugs or products such as paclitaxel from *Taxus baccata* and alkaloids from *Catharanthus roseus*, which are among eminent anticancer medicines basically derived from plants (Li-Weber, 2009; Newman et al., 2003). Traditional Chinese herbal medicine is nowadays utilised in the health care system of around 1.5 billion people globally (Dobos et al., 2005; Qi et al., 2013). Preferably, these medicines comprise a natural group to bring about the required medicinal outcome and decrease side effects (AZhang et al., 2013). In traditional medicine, a compound formulation or individual herb may consist of several plant chemical constituents, like flavonoids, alkaloids and terpenoids. In general, these constituents work alone or in combination with one another to bring about the desired medicinal effect (Parasuraman et al., 2014) (Table 12.1).

Table 12.1 Other Commonly Used Medicinal Herbs

Botanical names	*Family*	*Chemical constituents*	*Pharmacological uses*	*References*
Coriandrum sativum	*Umbelliferae/Apiaceae*	Cellulose, proteins, linalool, tannins, minerals, fibre, selenium, β-pinene, myrcene, α-thujene, limonene and sabinene	Anxiolytic, antidiabetic, antimicrobial, carminative, galactagogue, anthelmintic, antioxidant and spasmolytic activities	(Mahendra & Bisht, 2011)
Myrtus communis	*Myrtaceae*	Rich in flavonoids such as myricetin and gallocatechin derivatives, and terpenoids are also present	Anti-inflammatory, anti–*Helicobacter pylori*, antimicrobial, antiprotozoal, antidiabetic, anthelmintic, antioxidant, antidiarrheal and antimenorrhagial activities	(Sisay & Gashaw, 2017)
Prunus domestica	*Rosaceae*	Sorbitol, phenolics, high fibre content, anthocyanins, vitamins C, B, A, E and K	Anti-inflammatory, antioxidant, laxative, memory and cognition-enhancing effects	(Igwe & Charlton, 2016)
Linum usitatissimum	*Lineaceae*	Alpha-linolenic acid, ω-3 fatty acid, dietary fibres, lignans and proteins	Anti-atherosclerotic, antioxidant, anti-inflammatory, antidiabetic, antihypertensive, neuroprotective and cancer-preventing effects	(Parikh et al., 2019; Rajju Priya Soni et al., 2017)
Piper longum	*Piperaceae*	Methyl piperine, piperine, brachyamide-A, tetrahydropiperlongumine, pipercide, asarinine, longamide, piperidine, lignans, esters, tetrahydropiperic acid and palmitic acid, retrofractamide C, methylpiperate	Anticancer, anti-inflammatory, immunomodulatory, antifertility, anti-amoebic, antiobesity, analgesic, cardio-protective, hepatoprotective, antifungal and antioxidant activities	(Kumar et al., 2011)

(*Continued*)

Table 12.1 (Continued) Other Commonly Used Medicinal Herbs

Botanical names	*Family*	*Chemical constituents*	*Pharmacological uses*	*References*
Silybum marianum	*Asteraceae*	Silibinin A, silidianin, dehydrosilybin, silicristin, stearic acid, palmitic acid, silidianin, myristic acid, dihydroxysilibin, silibinin B, dianin, silybinom	Hepatoprotective, hypolipidemic, cardio-protective, cancer- and Alzheimer's disease–preventive activities	(Bahmani et al., 2015)
Terminalia chebula	*Combretaceae*	Phenolics including anthraquinones, chebulinic acids, corilagin, tannins, betasitosterol, amino acids, triterpenoids and gallic acids	Anticancer, antiviral, anti-inflammatory, anti-HIV, wound-healing, cardio-protective, and antimicrobial activities	(Kolla et al., 2017)
Cinnamomum cassia	*Lauraceae*	Cinnamaldehyde, camphor, linalool, camphene, β-pinene, cinncassiol A-G, glycosides, phenylpropanoids, lignans and lactones	Immunoprotective, analgesic, antibacterial, antitumour, cardio-protective, antiviral, antiobesity, anti-inflammatory, antidiabetic, neuroprotective and cytoprotective activities	(Zhang et al., 2019)
Tinospora cordifolia	*Menispermaceae*	Berberine, terpenoids, amritoside C, tinosporaside, steroids, tinosposinenside A, tinocordioside, cordioside, diterpenoids, amritoside B,	Antitumour, antimicrobial, antioxidant, anti-inflammatory, antiosteoporotic, antidiabetic and immunomodulatory effects	(Chi et al., 2016)
Glycyrrhiza glabra	*Fabaceae*	Chalcone, glycyrrhizin, isoliquiritigenin, glabridin, glycyrrhetic acid, flavonoids, tannins and alkaloids	Antiviral, antitussive, anti-inflammatory, expectorant, antitumour, wound-healing, immunomodulatory and antimicrobial properties	(Sharma et al., 2018)

Herbal medicines like *Asparagus racemosus*, *Tinospora cordifolia*, *Terminalia chebula*, *Emblica officinalis*, *Curcuma longa*, *Withania somnifera*, *Bacopa monnieri* and *Ocimum tenuiflorum* are strong immunity boosters (Balasubramani et al., 2011). Daily consumption of these herbal medicines, either alone or in the form of compound formulations like Brahma Rasayana and Chyawanprash, aids in the strengthening of the immune system and acts as efficient prophylaxis in the treatment of several infectious diseases such as COVID-19 infection (Nelaturi et al., 2021). Some of the most commonly used herbs are briefly described in this chapter, along with their safety evaluation and indications.

Withania somnifera (Ashwagandha)

Withania somnifera, also recognised as Indian ginseng, *ashwagandha* and winter cherry, belongs to the family *Solanaceae*, which is consumed as part of traditional medicine in lots of countries (Mishra et al., 2000). This herb is identified to manage impotency and enhance fertility, either consumed solely or in blend with other herbs (Mahdi et al., 2011; Sharma et al., 2011). Various plant parts such as leaves, seeds, fruits, roots and stems are utilised as a medicine in the traditional system of healing (Nasimi Doost Azgomi et al., 2018).

Chemical Constituents of WS

Numerous plant chemicals have been drawn out from this herb, holding various biological and therapeutic properties. *Ashwagandha* plant has been identified to consist of more than 80 kinds of plant chemicals such as glycosides, non-steroidal and steroidal alkaloids, anaferin, somnine, isopelletierine, withaferins, anthraquinones, hygrine, withanine, sitoindosides, cuscohygrine, anahygrine, somniferinine, withanolides, tropine, mesoanaferine (Direkvand-Moghadam et al., 2016; Krausz, 2011; Smith et al., 2008), hentriacontane, starch, pseudowithanine, iron, calcium, phosphorus, flavonoids, amino acids (such as glycine, alanine, glutamic acid, tyrosine, valine, aspartic acid, proline and cysteine) and volatile oil. Among all these constituents, sitoindosides and withaferin A had the main role in the therapeutic effects of *Withania somnifera* (Nasimi Doost Azgomi et al., 2018).

Pharmacological Uses of WS

Withania somnifera has been advised for treatment of asthma, polyarthritis, general weakness, ulcers, vitiligo, haemorrhoids, impotency, orchitis, painful swellings, leucorrhoea, premature ejaculation, uterine infections and oligospermia in traditional medicine. All of these medicinal uses propose its emmenagogue, anti-inflammatory, deobstruent and aphrodisiac properties. Various studies demonstrated that extracts of *Withania somnifera*, particularly of its roots, increase the quality of sperms, enhance its count and motility in men and, moreover, inhibit the toxic effects of chemicals on male and female gonads (Ambiye et al., 2013; Avicenna & Gruner, 1973; Gupta et al., 2013; Nasimi Doost Azgomi et al., 2018). It has the

Figure 12.1 *Withania somnifera.*

capacity to enhance the weight of gonads in both genders, increase spermatogenesis and folliculogenesis and make the levels of testosterone, leutinising hormone and follicle-stimulating hormones better (Al-Qarawi et al., 2000; Kumar et al., 2015; Nasimi Doost Azgomi et al., 2018). Moreover, Docking's research with *ashwagandha* (*Withania somnifera*) established four compounds, sitoindoside ix, withanoside iv, withanoside ii and withanoside V, that demonstrated possible reduction against a chief protein of SARS-CoV-2 (Tripathi et al., 2021).

Safety Evaluation of WS

The root extract of *Withania somnifera* was established to be free from any poisonous effects in subacute and acute studies of toxicology. Introducing the ethanolic, water-based, and hydro-alcoholic extracts of WS orally was stated practically safe in rats by these research studies. Extracts didn't give rise to any apparent signs of toxicity, unpleasant behaviour, stress or any modification in male rodents; nor did they present any modifications in intake of food, normal behaviour, serum bilirubin, body weight, ALT, ALP and AST levels (Mukherjee et al., 2021) (Figure 12.1).

Zingiber officinale

Zingiber officinale or ginger belongs to the family *Zingiberaceae* (similar to turmeric and cardamom) and is among the most frequently used herbs and flavouring agents all around the world (Surh, 1999). The spicy smell of ginger is primarily because of the existence of ketones, particularly gingerols, which emerge to be the principal

constituent of ginger researched in most of the health-associated scientific studies. The most consuming part of ginger is a rhizome which also has medicinal properties. Chinese and Indians are believed to have discovered ginger as a tonic for health more than 5,000 years ago to manage numerous diseases, and this herb is nowadays growing in all tropical regions, though India is its biggest producer (Bode & Dong, 2011).

Chemical Constituents of Ginger

Various analytical processes have identified nearly 115 constituents of dried and fresh ginger. Nearly 31 gingerol-associated constituents have been discovered from the crude alcoholic extracts of fresh rhizome of ginger (Jiang et al., 2005). Ginger has been divided into at least 14 bioactive constituents, including [8]-gingerol, methoxy-[10]-gingerol, [6]-shogaol, [6]-paradol, hexahydrocurcumin, 1-dehydro-[10]-gingerdioen, [14]-shogaol, [4]-gingerol, [10]-gingerdione, [6]-gingerol, tetrahydrocurcumin, [10]-gingerol, 1,7-bis-(4′hydroxyl-3′methoxyphenyl)-5-methoxyhepthan-3-one and gingerenone A (Koh et al., 2009).

Pharmacological Uses of Ginger

Ginger has been consumed for millennia for the management of several diseases, such as nausea, influenza, migraines, inflammation, arthritis and hypertension. A number of studies have reviewed the pharmacological and chemical properties of ginger (Bode & Dong, 2011). The ginger extract has been reported to have radioprotective (Jagetia et al., 2003), antitumour (Katiyar et al., 1996), antinausea, antirheumatic, anti-arthritic, anti-inflammatory, analgesic and pain-alleviating effects (Bode & Dong, 2011). Individuals suffering from knee osteoarthritis constantly demonstrated a better response to treatment with extract of ginger contrasted with the control group (Altman & Marcussen, 2001). The root of ginger is usually advised for the prevention of seasickness and is established to be better than placebo or dimenhydrinate against motion sickness (Mowrey & Clayson, 1982; Schmid et al., 1994). Ginger and its compounds are also documented to have antitumour properties (Katiyar et al., 1996).

Safety Evaluation of Ginger

Zingiber officinale is identified by the Food and Drug Administration of the United States as an additive for food that is GRAS (generally recognised as safe). One thousand milligrams per kilogram consumption of ginger extract orally was stated to be well tolerated by pregnant rodents, and it executed no side effects on fetal development (Weidner & Sigwart, 2001) (Figure 12.2).

Figure 12.2 *Zingiber officinale.*

Ocimum sanctum *(Tulsi)*

Ocimum sanctum or holy basil is commonly recognised as tulsi. The Sanskrit word tulsi indicates the 'incomparable one'. Tulsi is an extremely esteemed medicinal and culinary aromatic plant that belongs to the *Lamiaceae* family and is native to the Indian subcontinent. It has had its roots in Ayurveda for over 3,000 years, while in the medicinal system of Ayurveda, tulsi is often stated as a 'life elixir' for its healing potential and has been identified as managing lots of various common conditions of health. While the leaves' juice has been used as an eardrop, infusion of tea has been consumed for treatment of hepatic and gastric ailments and the stems and roots were also used traditionally to manage snake bites and malaria (Patel, 2020).

Chemical Constituents of *Ocimum sanctum*

The most frequently consumed tulsi plant part is its leaf, either fresh or dried, which is identified to consist of numerous bioactive constituents including 1,8-cineole, ursolic acid, linalool, eugenol and β -caryophyllene (Awasthi & Dixit, 2007; Bernhardt et al., 2015; Jamshidi & Cohen, 2017). Eugenol has been established to be the chief bioactive constituent mutually found in all kinds of tulsi with variable quantities in each cultivar, and it has currently been identified to perform by means of dual cellular methods to inhibit the levels of glucose in the blood (Anand et al., 2016; Singh et al., 2016).

Figure 12.3 *Ocimum sanctum.*

Pharmacological Uses of Tulsi

Several animal and in vitro research studies verify that the leaf of tulsi has strong pharmacological activities that include antidiabetic, immunomodulatory, adaptogenic, antimicrobial, antioxidant, metabolic, radioprotective, anticancer, hepatoprotective, and anti-inflammatory effects that have been previously reviewed extensively. Identically, current research states that water-based and alcoholic extracts of tulsi protect rodents from stress-persuaded cardiovascular modifications. While animal model studies have further demonstrated that the tulsi leaf extract holds anxiolytic and anticonvulsant properties. A number of animal studies carried out over more than the past 50 years state that consumption of tulsi leaves makes the lipid and glucose profiles better in both diabetic-induced and normal animal models. Meanwhile, the intramammary infusion of water-based tulsi leaf extract has also demonstrated an encouraging effect on enhancing the immune reaction in bovine animal models (Jamshidi & Cohen, 2017).

Safety Evaluation of Tulsi

All of the reviewed studies documented positive clinical outcomes with little or no adverse effects, regardless of formulation, gender or age of the research participant and the dose, with merely one of the research trials documenting mild nausea for a short duration. The long-established history of using holy basil on a daily basis doesn't report any serious long-term outcomes and therefore tulsi is determined as safe (Jamshidi & Cohen, 2017; Satapathy et al., 2017) (Figure 12.3).

Asparagus Racemosus (Shatavari)

One of the most famous adaptogens, *Asparagus racemosus*, is categorised as Rasayana, a herb that improves vigour, vitality and immunity (Govindarajan et al., 2005; Rege et al., 1999). A part of the family *Asparagaceae*, previously *Asparagus racemosus*, has been revealed to stimulate antioxidant, antibacterial, antitussive,

immunomodulatory and antihepatotoxic effects in both human and rodent models (Alok et al., 2013). The therapeutic usage of the *shatavari* plant has been documented in British and Indian pharmacopoeias and traditional medicinal systems. The word *shatavari* factually means 'capable of possessing [a] hundred husbands' and capacity to provide strength to reproductive health so that females can give rise to healthy ova. Asparagus has also been consumed to enhance fertility and vitality. In the traditional medicinal system, *shatavari* has been perceived as one of the most significant herbs, typically advised for providing nourishment to ovaries, maintaining sexual desire in women and enhancing the synthesis of reproductive hormones (Pandey et al., 2018).

Chemical Constituents of *Asparagus racemosus*

Asparagus has more than 50 natural constituents, including isoflavones, glycosides, mucilage, alkaloids, saponins, polysaccharides, steroidal and racemosol. The steroidal saponins are active biological compounds of asparagus root. Glycosides of quercetin and flavonoids are present in fruits and flowers, while quercetin-3-glucuronide is established in asparagus leaves. Numerous other bioactive constituents like asparagamine (Pandey et al., 2018; Sekine et al., 1994), kaempferol and racemosol are drawn out from the alcoholic root extract of asparagus (Negi et al., 2010; Pandey et al., 2018). The primary plant chemicals established in *shatavari* include saponins, like shatavarin VII and shatavarin VI, as well as racemofuran, asparagamine A and racemosol. Steroidal saponins are a varying class of glycosides whose constitutional complexity results in a broad range of chemical and biological properties that may be a cause of benefits related to herbal drugs (Anders et al., 2020).

Pharmacological Uses of *A. racemosus*

Asparagus is well known to enhance longevity, improve mental activity, prevent ageing and add vitality and vigour to the body (Alok et al., 2013). It is extremely effective in disorders of the female reproductive tract (Alok et al., 2013; Singh et al., 2012). *Shatavari* has been advised for the management of several ailments such as cough, rheumatism, headache, piles, problems with the gastrointestinal tract, gonorrhoea, diabetes and diarrhoea (Singh & Geetanjali, 2016). It makes the function of ovaries better and enhances the weight of the uterus and levels of oestrogen in rodents. The antiulcer, anticoagulant, antifungal, antioxidant, anticancer, antibacterial, anti-abortifacient, antidysenteric and anti-inflammatory activities of *Asparagus racemosus* have been documented in clinical trials and in experimental animals (Pandey et al., 2018).

In Ayurveda, asparagus has been used extensively for the management of stress-associated immune diseases and to make the general conditions of health better (Alok et al., 2013; Singh & Geetanjali, 2016). Intake of alcoholic extract of asparagus orally (regularly for 15 days) applies oestrogenic impact on the mammary glands of females as well as reproductive glands in pregnant (adult) rodents (Pandey et al., 2005). Asparagus is also beneficial in threatened abortions because of the presence of steroidal saponins, which also block the uterine contractions induced by oxytocin in rodents, guinea pigs and rabbits in situ as well as in vivo (Pandey et al., 2018).

Figure 12.4 *Asparagus racemosus*.

Safety Evaluation of *Shatavari*

Prolonged intake of asparagus does not demonstrate any abnormality, toxicity, teratogenic effects or changes in the behaviour of animals (particularly rodents) (Goel et al., 2006) (Figure 12.4).

Emblica officinalis

Emblica officinalis, also recognised as *Phyllanthus emblica*, emblic myrobalan, Indian gooseberry or *amla*, belongs to the *Euphorbiaceae* family. *Amla* is one of the most frequently used medicinal herbs in the traditional system of medicine and has been consumed as a nutritious tonic and medicine for having vitamins and essential amino acids. It is predominantly a major source of minerals and vitamin C contrasted with other citrus fruits. Though all parts of emblic myrobalan are consumed for therapeutic reasons, the fruits are used more extensively as Rasayana, either solely or in blend with other herbs for the management of numerous contagious or non-contagious diseases. The fruits of *Emblica officinalis* are broadly utilised as antipyretic and anti-inflammatory medicine apart from its typical consumption as a tonic during the season of winter (Ihantola-Vormisto et al., 1997; Srivasuki, 2012).

Chemical Constituents of *Emblica officinalis*

Emblica officinalis is well identified for containing several nutrients and is also comprised of a range of chemical compounds, including phenolic glycosides, carbohydrates, phenolic acids, alkaloids, tannins, flavone glycosides, sesquiterpenoids, aminoacids, norsesquiterpenoids and mucic acid (Variya et al., 2016). The juice of *amla* consists of the greatest quantity of vitamin C, around 478.56 milligrams per 100 ml in contrast with other fruits, like Pusa Navrang grape, apple, lime, Perlette grape and pomegranate (Jain & Khurdiya, 2004; Tarwadi & Agte, 2007). Synergic acid, caffeic acid, coumaric acid and myricetin are established to be found in both

Figure 12.5 *Emblica officinalis.*

seeds and pulp, while quercetin and gallic acid are established to be present in pulp only rather than the *amla* seed (Nambiar et al., 2015).

Pharmacological Uses of *Amla*

Emblica officinale has been stated to have antioxidant, antiproliferative, anticancer, antimutagenic, hepatoprotective, antidiabetic, antihypercholesterolemic, anti-atherosclerotic, antitriglyceride, cardio-protective, adaptogenic, analgesic, anti-inflammatory, antipyretic, antimicrobial, immunomodulatory and wound-healing properties. The antioxidant activity was ascribed to vitamin C–like chemicals which are gallic acid, emblicanin A, punigluconin, emblicanin B and pedunculagin (Variya et al., 2016).

Safety Evaluation of *Amla*

The outcomes of various studies propose that consumption of *amla* may provide lots of benefits to the body without affecting renal or hepatic functions in healthy individuals. The outcomes from one of the research studies established that *amla* has adequate safety and sensory profile while giving huge potential for treatment (Kapoor et al., 2020) (Figure 12.5).

Lavandula stoechaes

According to Upson, other names of *Lavandula* L are: *Isinia rech* F., *Sabaudia Buscal*, *Stoechas* Mill, *Sabaudia Muschl*, *Chaetostachys Benth* and *Fabricia Adans*. The genus of *Lavandula* is comprised of around 39 species, numerous hybrids and approximately 400 cultivars that are already registered (Upson et al., 2004). The flowers of plants are lilac or pink, blue, purple or violet in colour. Among other species, *Lavandula stoechaes* was probably the first to be utilised for extracting essential oils. The Arabs, Greeks and Romans all identified therapeutic properties of lavender. It is also utilised for the synthesis of cosmetic products, herbal decoctions and

traditional dishes. The phytopharmacological and ethnobotanical studies revealed that in Morocco, it is used to manage inflammatory conditions, nephrotic syndrome, spasm, pain and rheumatic disorders (Ez Zoubi et al., 2020).

Chemical Constituents of Lavender

A number of phenolic constituents have been recognised in the genus of *Lavandula*, including luteolin, quercetin, ferulic, pinobanskin, protocatechuic, rosmarinic acids, caffeic acid, pinocembrin and chlorogenic acid (Lee et al., 2011). Among the several chemical constituents identified in *Lavandula stoechas*, Ez Zoubi et al. (2016) showed the existence of many classes of chemicals in the alcoholic extract, like mucilages, sterols, flavonoids, catechic tannins, leucoanthocyans and coumarins. *Lavandula antineae Maire* was established to synthesise tannins and flavonoids, and *Lavandula officinalis* was established to consist of coumarins. The studies identified the existence of luteolin 7-glucuronide, apigenin 7-glucoside, luteolin 7-glucoside and luteolin (Ez Zoubi et al., 2020).

Pharmacological Uses of Lavender

A number of researchers worked on the medicinal uses of *Lavandula stoechas* extracts and essential oils and have identified their antileishmanial, antifungal, insecticidal and antimicrobial activities (Yassine et al., 2017). *Lavandula stoechas* also has favourable effects on eczema, wounds and urinary tract infections; moreover, it has antiseptic, sedative and analgesic properties. It is also consumed as a cooking herb to make a specific kind of couscous, to enhance the flavour of particular traditional dishes and to make soup and tea. In a few countries like Tunisia, Algeria and Morocco, this herb is discussed in the classical *Pharmacopoeia of Medicine* to manage rheumatic diseases, inflammatory disorders, headaches, diabetes and depression (Ez Zoubi et al., 2020). In Palestinian regions, lavender decoction is consumed to manage epilepsy and migraine (Gilani et al., 2000) since it has anti-inflammatory and antioxidant activities. The infusion of a flower is consumed in Turkish plant therapy as a carminative, stimulant, resolvent, cicatrisant for wound healing, antispasmodic, deobstruent and expectorant (Ez Zoubi et al., 2020; Giray et al., 2008). Moreover, the camphor, which is one of the chief compounds identified in the essential oil of *Lavandula stoechas*, is recognised to have insect-killing activities (Maia & Moore, 2011; Mazyad & Soliman, 2001).

Safety Evaluation of *Lavandula stoeachas Linn*

Studies regarding acute toxicity of AfL.s (active fraction of *Lavandula stoeachas*) specified that the plant, if consumed in large doses (greater than 400 mg/kg per oral), can result in seizures, hyperactivity, ataxia, hyperstimulation and sudden death. These harmful effects are because of the great doses of phenethylamine, which may have potentially toxic effects and are accountable for seizures, confusion, headaches, hallucinations and subsequently death in humans (Nelson et al., 2014). Tremors, headache, restlessness, aggression and diarrhoea are minor adverse effects, which may be noticed with the phenethylamine overdoses. Previous studies

Figure 12.6 *Lavandula stoechas.*

have stated that extremely toxic doses of phenethylamine (around 125–200 mg per kilogram intra-peritoneal) produced serious seizures and, at last, death because of the hyperstimulation of the brain and cardiac arrest. The LD50 for the active fraction of *Lavandula stoechas* was measured as 325 mg per kilogram per oral, which specified that it had an extensive pharmacological index (Dourish & Cooper, 1983; Mushtaq et al., 2021) (Figure 12.6).

Vaccinium macrocarpon *(cranberry)*

Cranberry fruit or *Vaccinium macrocarpon* is categorised as a functional food because of its naturally present high-quality constituents, like polyphenols, thought to have health-enhancing and antioxidant properties (Szajdek & Borowska, 2008). The documented health benefits of consuming cranberry vary from its gastroprotective to cardio-protective effects. It also helps in improving the levels of cholesterol in the blood (Pappas & Schaich, 2009; Ruel et al., 2006). Cranberry can be found in different forms, such as dried or fresh fruit, capsules or tablets of cranberry extract and cranberry juice. Extract of *Vaccinium macrocarpon* could be a possible substitute for antibiotics to manage uncomplicated but acute urinary tract infections (Gbinigie et al., 2020).

Chemical Constituents of Cranberry

Vaccinium macrocarpon has several compounds and rich composition of plant chemicals, especially A-type procyanidins, benzoic acid, flavan-3-ols, ursolic acid and anthocyanins. Flavan-3-ols in cranberry exist as polymers, oligomers and monomers. Quantities of anthocyanins are significantly high in cranberry, giving colour to the fruits and associated food items, as well as the possible outcomes on

Figure 12.7 *Vaccinium macrocarpon* (cranberry).

the health of humans. Cranberry also consists of hydroxycinnamic and hydroxybenzoic acids. Ursolic acid is plentiful in American cranberry at around 46 to 109 mg per 100 grams of fresh weight. This constituent is present in several herbs and has potent anti-inflammatory activities. Flavonols in *Vaccinium macrocarpon* primarily comprise glycosides of myricetin, quercetin and, to a lesser degree, kaempferol (Blumberg et al., 2013).

Pharmacological Uses of Cranberry

Lots of mechanisms are responsible for the beneficial outcomes of cranberry intake on CVD (cardiovascular disorders), including its impact on risk factors of cardiovascular diseases like oxidative stress, the function of platelets, dyslipidemia, hypertension, arterial stiffness, inflammation, diabetes and endothelial dysfunction. Such beneficial effects might inhibit lesion progression, thrombosis, atherogenesis, ischaemic cardiomyopathy, plaque rupture and myocardial infarction. A number of studies and two meta-analyses stipulate a benefit of consuming cranberry in inhibiting the relapse of urinary tract infections (Blumberg et al., 2013).

Safety Evaluation of Cranberry

Possible harmful effects related to the consumption of cranberry, though, must be contemplated. There is mixed verification of a relationship between warfarin and cranberry (Choi et al., 2017) and a relationship with urolithiasis (Gettman et al., 2005) (Figure 12.7).

Aloe barbadensis

Aloe vera has a long-established history of providing a multitude of benefits for health and is amongst the most commonly utilised natural remedies all around the globe. *Aloe barbadensis* is the most famous and extensively utilised species. Aloe is originated from the Arabic term *alloeh* which means ‘bitter and glossy substance’, while vera is derived from the Latin term ‘truth’. Aloe vera belongs to the family *Liliaceae* and is an extremely little stemmed or stemless xerophyte with peaked and elongated leaves in which great quantities of water are reserved in the tissues

(Boudreau & Beland, 2006). In early Egypt, aloe vera was recognised as the 'immortal plant' and has been consumed as a traditional medicinal herb in Roman, Greek, Arab, Korean, Egyptian, Japanese, Chinese and Indian cultures (Atherton, 1998; Grindlay & Reynolds, 1986).

Chemical Constituents of Aloe Vera

The aloe vera pulp comprises nearly 98.5% water, whereas the gel or mucilage comprises about 99.5% water (Atiba et al., 2011). The other 0.5 to 1% of solid content comprises a variety of constituents, including fat-soluble and water-soluble vitamins (vitamin E, B1, B6, B2, B9, C, choline, β-carotene), enzymes, phenolic constituents, minerals (zinc, sodium, calcium, magnesium, copper, phosphorus, chlorine, iron, potassium, chromium and manganese) organic acids and polysaccharides (Food and Drug Administration, 2002). The bitter yellow exudate consists of 1,8-dihydroxyanthraquinone compounds and their glycosides, which are used primarily for their purgative effects (Grosse et al., 2013).

The Pharmacological Activity of Aloe Vera

Aloe consists of therapeutically active constituents related to a range of biological effects, including antiviral, anti-inflammatory, laxative, fungicidal, antibacterial, immunomodulating and antimicrobial activities (Cosmetic Ingredient Review Expert Panel, 2007). It has been used for hundreds of years to empirically manage a wide range of diseases like diabetes, ulcers, skin ailments, including (burns and psoriasis), hyperlipidemia, SLE and constipation. Aloe vera synthesis has been a rising industry for manufacturing functional food, laxative medicines and cosmetics like cleansers, lotions, toners, makeup, wipes, shampoos, foundations, creams, shaving creams and hand creams (Guo & Mei, 2016).

Figure 12.8 Aloe vera leaf.

Safety Evaluation of Aloe Vera

The USFDA stated a final regulation mentioning that utilisation of aloe vera as a non-prescribed purgative medicine is no longer GRAS and efficient (Food and Drug Administration, 2002). Currently, the whole aloe vera leaf extract has been categorised by the international cancer research agency as a prospective carcinogen for humans along with other herbal medicines such as kava extract and ginkgo biloba extract (Grosse et al., 2013; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2016). Prolonged use of anthranoid laxatives might be associated with the risk of growing colon carcinoma (van Gorkom et al., 1999). The International Council of Aloe Science proposes that the highest permitted content of aloin in aloe-originated material for oral intake is below ten parts per million (PPM); for non-therapeutic consumption, the advised limit is 50 or lower parts per million (Guo & Mei, 2016) (Figure 12.8).

Trachyspermum ammi

Trachyspermum ammi is a long-established herb with several medicinal properties; the herb is commonly known as *ajwain*, carom seeds, *kammun*, bishop's seeds and *al-yunan*. It belongs to the family *Apiaceae*. In traditional and medieval periods, the oil of *Trachyspermum ammi* was reported to be used in neurological diseases such as palsy, persistent pain, tremors and paralysis. Formerly the *ajwain* extract has been used to treat ear and eye infections. Seeds of *ajwain* were recognised to be effective against gastrointestinal and pulmonary diseases. *Ajwain* was also documented as a diuretic, aphrodisiac and galactagogue. The practitioners of Persian medicine also stated the use of *Trachyspermum ammi* (seeds) in fumigation for disorders of the female genital tract (Moein et al., 2015).

Chemical Constituents of *Ajwain*

Studies of *Trachyspermum ammi* seeds demonstrate that it consists of 38.6% carbohydrate, 18.1% fat, 15.4% protein, 11.9% fibre, 8.9% moisture, 7.1% mineral matter (such as iron, calcium, phosphorus), glycosides, tannins, flavones and saponins (Pruthi, 2011). Significant constituents of *Trachyspermum ammi* include dillapiole (9%), limonene (38%) and carvone (48%), while essential oil of *Trachyspermum ammi* consists of thymol (35–60%) as its chief constituent. The rest of the non-thymol constituents are known as thymine which consists of β-pinene (4–5%), limonene with β-pinene and γ-pinenes (30–35%) and p-cymene (50–55%). The fruit of *ajwain* consists of lots of minerals like lithium, cadmium, aluminium, iron, calcium and copper. Furthermore, zinc, manganese, chromium, nicotinic acid, phosphorus, riboflavin, cobalt, thiamine, calcium, copper, carotene, iron and iodine were also established in the fruit (Asif et al., 2014).

Pharmacological Uses of *Ajwain*

The oil drawn out from *ajwain* has demonstrated significant analgesic, antifungal, antiviral, antibacterial, anti-inflammatory and antitussive effects as well as bronchodilatory, antioxidant and antitumour activities (Moein et al., 2015). The carvacrol, thymol and phenols are accountable for the expectorant, antitussive and antiseptic activities. *Trachyspermum ammi* has also been used traditionally as a milk-enhancing agent in

Figure 12.9 *Trachyspermum ammi.*

humans. Generally, thymol is identified for its antibacterial activities. Thymol is typically integrated into mouthwashes because of its antimicrobial activity against bacteria in the oral cavity (Asif et al., 2014). It is utilised as vermifuge, spasmogenic, lactagogue, fungicide, diaphoretic, aphrodisiac, carminative, hypotensive, antiseptic, tonic, litholytic, gastrostimulant, emmenagogue, cardio depressant, antispasmodic, diuretic, gastro relaxant, expectorant, laxative, sialogogue and stomachic (Duke, 2001).

Safety Evaluation of *Trachyspermum Ammi*

In general, *Trachyspermum ammi* is considered safe when consumed in the prescribed doses, though it can be the reason for headaches and nausea in some individuals. The safety of *ajwain* in patients with kidney and hepatic ailments, children, pregnant or nursing women is not documented well. If used with supplements or herbs that have an impact on the aggregation of platelets, like garlic, red clover, white willow, ginger, angelica, turmeric and *danshen*, *ajwain* may enhance the bleeding risk (Bown, 2001; Grossberg & Fox, 2007) (Figure 12.9).

Elettaria cardamomum

Cardamom belongs to the family *Zingiberaceae*; it is a commercially important and high-priced spice globally in demand. Though it is native to Sri Lanka and India, it is also cultivated in Tanzania, Guatemala, Laos, the Malay Archipelago, Thailand, Cambodia, El Salvador and Papua New Guinea, with Guatemala being the greatest producer of cardamom in the world (Aghasi et al., 2018; Cyriac et al., 2016). According to the ancient Ayurvedic literature, cardamom spice has been used to assist digestion and reduce fat. Egyptians of previous times consumed *Elettaria cardamomum* as a refresher for the mouth. In Indian cuisine, cardamom is extensively utilised as a spice. Fruit is the most consumable part of the plant, while its essential

oils and seeds are utilised as flavouring constituents in a range of edibles, including meat and its products, baked food, beverages, condiments, candy and desserts. Ancient Egyptians masticated cardamom seeds to enhance the whiteness of their teeth, and ancient Greeks imported them till the fourth century BC; the Greek physician of the first century, Pedanius Dioscorides, mentions cardamom in his book *De Materia Medica* (Sengottuvelu, 2011).

Chemical Constituents of Cardamom

The estimated composition of cardamom includes fat 2.4%, ash 5.3%, protein 10.6% and carbohydrate 68.2%. A hundred grams of cardamom consisted of around 13 mg of iron, 100 mg of sulphur, 93 mg of calcium, 124 mg of potassium, 182 mg magnesium and 183 mg of phosphorus. All of these minerals are indispensable micronutrients for regular physiological activities in humans. Leaves and capsules of cardamom consist of considerable levels of copper, zinc and manganese (Ashokkumar, Murugan, et al., 2020; Ereifej et al., 2015). Ashokkumar et al. documented nutritionally significant cardamom metabolites that consist of carotenoids (β-carotene and lutein) and flavonoids (kaempferol, myricetin, catechin and quercetin) (Ashokkumar, Pandian, et al., 2020). Essential oil of cardamom primarily has monoterpene compounds like α-terpinyl acetate, linalool, α-pinene, 1,8-cineole, α-terpineol, linalyl acetate, ester compounds and nerolidol, all of which have medicinal uses including gastroprotective, antidiabetic, antioxidant, anti-inflammatory, antiviral, anticancer and antifungal activities. Current research studies claimed that phenolic compounds, terpenoids and flavonoids were being utilised for managing pulmonary, cardiovascular and kidney-related diseases (Ashokkumar, Murugan, et al., 2020).

Pharmacological Uses of Cardamom

Cardamom has been utilised as traditional medicine and culinary herb for hundreds of years. Its uses include renal diseases, asthma, periodontitis, gastrointestinal issues, gum infections (Hamzaa & Osman, 2012; Saeed et al., 2014), nausea, cardiac diseases, cataracts and diarrhoea (Gilani et al., 2008; Khan et al., 2011). The activities and usage of cardamom as functional food, nutraceutical and phytopharmaceutical are because of its bioactive constituents and essential oil (Hamzaa & Osman, 2012). Cardamom has been utilised from the fourth century by ancient Roman and Greek doctors and Indian Ayurveda physicians to manage several health conditions like constipation, asthma, bronchitis, CVD, cold, chest congestion and pulmonary tuberculosis. In TCM, cardamom was used to manage dysentery, constipation, bladder infections and stomach ache in children; it has also been extensively used in Ayurveda to manage food poisoning (Ashokkumar, Murugan, et al., 2020).

Safety Evaluation of Cardamom

In classical medicine, cardamom is considered harmless, owing to its prolonged consumption as a natural remedy and common culinary herb in different food products and drinks. No toxicity or side effects are documented in the text. Though a few reports show cardamom seeds can provoke gallstone colic, they are not advised in people with gallstones (Sengottuvelu, 2011) (Figure 12.10).

Figure 12.10 *Elettaria cardamomum*.

Cardio-Protective Effects of Herbs

Cardiovascular disorders are initiated by many factors like an increased aggregation of platelets, high cholesterol and high blood pressure. A decrease in levels of LDL cholesterol is regarded as significant to inhibit the risk of myocardial infarction (Rahman, 2007). A number of plants and their active constituents have been related to inhibiting the levels of low-density lipoprotein, including curcumin, garlic, fenugreek, lemongrass, onion, ginger, capsaicin and cinnamon (Akhani et al., 2004; Srinivasan, 2006; Srinivasan et al., 2004; Tapsell et al., 2006). Garlic has been related to a reduction in blood pressure (Rahman, 2007). There is verification to propose that curcumin can decrease cerebral vasospasm, vascular inflammation and other post-stroke complications while also preventing stroke (Singletary, 2010).

Antimutagenic and Apoptotic Activity of Various Plants

Decreasing the mutagen's activity can be one of the most significant methods to prevent the development of carcinogenic events. The extracts of black pepper, coriander and caraway, essential oils of eugenol, cumin xanthoxylum, nutmeg, cardamom, black pepper, celery, ginger and coriander and the juice of mustard and coriander have been noticed to decrease mutagenicity. Apoptotic induction in cells of the tumour is a promising medicinal approach. Natural apoptotic moderators may play a significant role in cancer prevention. Allicin has been demonstrated to persuade apoptosis of different malignant cells in humans, including skin, breast, prostate, colorectal, lymphoma, bladder and hepatic tumour cell lines. Ajoene has decreased multiplication and prompted apoptosis of leukaemia cells in humans. Garlic extract, protodioscin, cinnamaldehyde, diosgenin, 1,8-cineole and isothiocyanates are efficient in inducing apoptosis of several cancer cells in humans. Flavonoid apigenin commonly found in lettuce, celery and parsley, allicin from garlic, diallyl sulphide from allium and curcumin have also been observed to induce cancer cell apoptosis in humans (Peter, 2012; Rahman, 2007).

Anti-Inflammatory Effects of Herbs

Estimates proposed that around 15% of all cancers are associated with proinflammatory mediators like leukotrienes, chemokines, nitric oxide, cytokines and prostaglandins, which disturb the regular signalling inside the cells (Surh et al., 2005). In vitro research revealed that bioactive constituents in numerous spices and herbs can decrease inflammatory effects (Hollman & Katan, 1999). These constituents which decreased the expression of COX-2 include salicylic acid (found in cumin, paprika and turmeric), curcumin and delphinidin (found in pomegranate) (Aravindaram & Yang, 2010; Kaefer & Milner, 2008). Nitric oxide is one of the inflammatory mediators involved in the development of cancer which is decreased by bioactive constituents within spices and herbs. Rosemary has been established to be most efficient in impeding the synthesis of nitric oxide, followed by thyme, basil, tarragon, oregano, marjoram and cinnamon (Tsai et al., 2007). Nitric oxide is closely associated with the pathway of NF-kB. Bioactive constituents, quercetin (commonly established in fennel, cumin and basil), gingerol (in ginger), ursolic acid (in rosemary and basil), curcumin and capsaicin, decrease the in vitro and in vivo pathway of NF-kB (Peter, 2012).

Common Medicines from Animal Products

Animals have been consumed as a source of medicine by humans for thousands of years. These primaeval practices were reported in the historical literature of the Mediterranean region like *De Materia Medica* of Dioscorides and carry on to be reported even in ethnobiological studies in the current era. Animals and their products have accounted for a considerable segment of the pharmacopoeia of the Mediterranean region. Simultaneously identified today as zoomedicinal remedies, a number of these ancient treatment approaches have existed in traditional medicinal practices of the current era and even get combined into pharmaceutical practices of modern times. The Ebers papyrus (an ancient Egyptian text) includes therapeutic discussions of animals and their products such as the glands of musk deer, the blood of lizards, the sperm of whales and honey among others (Bryan, 1974; Lev, 2006; Nunn, 1996). Animals have visibly played a key role in the therapeutic pharmacopoeia of humans for at least millennia. Nowadays, animal-based drugs keep playing a significant role in various traditional systems of medicine globally, as well as in recent pharmaceuticals. A few examples include ω-3 supplements of polyunsaturated fatty acids prepared by recognised fish oils (Costa-Neto, 2005) and ACE inhibitors from viper snake venom (Bisset, 1991). Some of the animal products that are commonly used as medicines are discussed in the following sections.

Bombyx Mori*/Silk Cocoon*

Silk cocoon or silkworm belongs to the family *Bombicidae* and is fundamentally native to the land of China; however, for a long time it has been tamed all around the globe extensively in the subtropical and temperate regions for its high-quality cocoon threads. Meanwhile, its larvae have been recognised as a prospective source of AKH (adipokinetic hormone), amino acids, inhibitors of chymotrypsin, sex pheromone, bombykol and b-N-acetyl glucosaminidase etc. Besides their health values, particularly for polyps, diabetes, trigeminal neuralgia, cardiovascular disorders,

vocal nodules, bronchial asthma, pain and the management of facial paralysis, the pupae of silk cocoon are a source of amino acids, vitamin B2, proteins, diapause hormone, vitamin E and B1. They contribute a segment of antihistaminic and antimicrobial compositions. The male moths are utilised to manage infertility. Carotene, chlorophyll, solanesol, pectin, triacontanol and phytol drawn out from the faeces of silkworm are utilised in the management of several disorders like leukocytopenia acute pancreatitis, gastric disorders, hepatitis and nephritis. Carotene is utilised in the compounds of vitamin A, while phytol is utilised in vitamin K and E. As a source of vitamins and animal proteins, the pupae and larvae are of low cost and available in large quantities. If treated appropriately, it should somewhat address the deficiency of protein in rural regions. The pupae, larvae and their by-products are also used to manage common diseases of urban areas such as high BP, diabetes, ulcer, cardiac diseases, bronchial asthma, hepatitis, high blood cholesterol and other geriatric diseases (Singh & Jayasomu, 2002).

Fish Oil

Fish oil's effects in the prevention and treatment of diseases have been researched for more than 50 years. Fish oils, which are loaded with fatty acids, demonstrate proof of possible health benefits (Rodríguez-Cruz & Serna, 2017), including medicinal and cosmetic applications of fatty acids from fish oil on the skin. Huge amounts of PUFAs are derived from fish oil extracts, among which EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) are the predominant polyunsaturated fatty acids. The attraction towards fish oils has grown from the documents on Inuits' high consumption of fish oils in diets related to an extremely low frequency of inflammation-associated disorders and ischaemic cardiac ailments (Fodor et al., 2014). The polyunsaturated fatty acids in fish oils have been established to be useful for managing asthma, cancers, rheumatoid arthritis, Parkinson's disease, psoriasis, diabetes mellitus, depression, colitis, cardiovascular disorders and osteoporosis (Villani et al., 2013). Polyunsaturated fatty acids also show beneficial effects on the development of cutaneous, immune, nervous and visual systems in infants (Wu et al., 2014). The research studies demonstrate a considerable improvement in patients with asthma symptoms receiving supplements of fish oil loaded with EPA and DHA (Hardy et al., 2016). The consumption of fish oil packed with ω-3 fatty acid has been related to the inhibition of plasma triglyceride concentration, giving rise to the decreased frequency of hyperlipidemia (Eslick et al., 2009). The supplementation of polyunsaturated fatty acids can decrease the risks of cardiovascular and associated diseases like high BP, thrombosis and hypercholesterolemia. Further meta-analysis has revealed that consumption of fish oil and ω-3 polyunsaturated fatty acids diminishes the risk of developing type 2 DM by increasing sensitivity to insulin. The intake of fish oil consisting of great levels of polyunsaturated fatty acids can play a role in preventing and managing cancer (Huang et al., 2018).

Earthworm

The earthworm is enriched with nutrients and macromolecules and has long been consumed as an edible among different indigenous cultures (Cooper et al., 2012). Earthworms' medicinal and nutritional value has been used for hundreds of years

among complementary and traditional practices such as Kampo, Ayurveda, traditional Chinese medicine and Korean medicine, from which contemporary knowledge of the medicinal properties of earthworms comes. Earthworm and its products show anti-inflammatory properties and pledge to manage coagulation-related diseases in humans (Cooper, 2014; Cooper et al., 2012). Their capacity to revitalise lost projections has further prompted research in its utilisations in mammals, particularly by increasing the capacity of regeneration to revitalise the damaged nerves. The medicinal and nutritional benefits of earthworms and their influence on chronic conditions in humans are closely bound to understanding innate immunity development (Cooper & Hirabayashi, 2013). The innate immunity of earthworms has currently been investigated by means of profiling genes of earthworm's leukocytes which play a considerable role in immunity. Investigations of demonstrated sequence tags give rise to recognition of cell defence and immune-associated genes, giving beneficial knowledge for future research that emphasises the immune systems of earthworms (Tak et al., 2015). Constituents originating from earthworms have the power to give innovative management for diseases like thrombosis. For instance, analysis of earthworm constituent lumbrokinase has demonstrated its efficiency as powerful management of blood clots, with the detoxification of an individual lumbrokinase enhancing its antithrombotic effects and sequentially making the general utilisation of lumbrokinase better (Li et al., 2012).

Scorpion Venom

Despite the life-threatening and hazardous outcomes of scorpion envenoming, the healing properties of scorpion venoms and body parts in traditional medicine have been recognised by humans for millennia (Petricevich, 2010). It is extensively documented in the texts that scorpion venom is enriched with bioactive constituents, and as such, the toxin of scorpions is of great interest to the medicine-making industries (Kerkis et al., 2017). Despite the fact that significant research efforts are kept going, and the likelihood for scorpion-originated medicinal peptides is extremely promising, the only toxin that has been chosen for clinical studies from the venom of the scorpion is chlorotoxin (Ahmadi et al., 2020).

Common Medicines from Minerals

Coral

Corals belong to phylum Cnidaria and can usually be classified into gorgonian, soft or hard type organisms. Coral is one of the sources of diterpenes that have been demonstrated to reveal medicinal properties, particularly anti-inflammatory, which is one of the distinct therapeutic uses that have been established to be promising principally in association with natural coral products for arthritis. One distinct coral genus has an organic metabolite, revealing considerable anticarcinogenic effects. The cembranes and lobanes were experimented on for their anticancer effects against three cancer cell lines in humans and demonstrated a 50% reduction in the growth of tumours. It has been utilised as a silicon source to decrease BP and make the expression of genes better that enhanced the health of the cardiovascular

system in hypertensive rodents (Maehira et al., 2011). Moreover, Chen et al. drew out a brain-protective constituent, 11-dehydrosinularolide, from a coral which they think could be utilised to manage Parkinson's disease (Chen et al., 2012).

Hajrul Yahood (Lapis judaicus)

Hajrul yahood or *Lapis judaicus* is a mineral-origin medicine. It is commonly recognised by the name Jew's stone and is established in the geological stratum of the Jurassic era (millions of years ago) (Lev & Dolev, 2002). *Hajrul yahood* had been utilised as a diuretic and to manage lithiasis and obstruction in the urinary tract since the era of the Romans (Lev & Dolev, 2002). Ibn al Baytar wrote that Galen claimed it to be an experimented medicine in managing kidney stones; however, it was not established to be beneficial in patients with cystolithiasis (Makbul et al., 2018). Ethnomedicinal studies demonstrated that in local markets of Jordan, it is sold as a chief pharmacological ingredient for managing nephrolithiasis (Lev & Amar, 2002). It dissolves both bladder and kidney stones; its powder manages wounds and, when blended with honey, soothes the hard skin and calluses (Saad & Said, 2011). It has been mentioned in Avicenna's *Canon of Medicine* as a mineral drug for dissolving and eradicating bladder and kidney stones (Avicenna & Gruner, 1973; Makbul et al., 2018).

Safoof e Habis

Safoof e habis is the compound herbomineral formulation prepared by combining *Vateria indica* L (*raal sufaid*), magnesium silicate (hydrated), silicate of alumina and iron oxide. This composition has astringent and styptic properties and has been consumed for many years to manage menorrhagia. *Vateria indica* L consists of tannin (Fathima & Sultana, 2012), which thickens the proteins in cells and blanches or contracts endothelium of capillaries, therefore decreasing the quantity of blood loss during menstruation (Kennedy et al., 1984). *Vateria indica* L, silicate of alumina and iron oxide also consist of calcium that assists in preserving the mechanism of hemostasis, while hydrated magnesium silicate increases blood coagulation (Fathima & Sultana, 2012).

Conclusion

The nature-based products acquired either from different minerals, microbes, animals or plants in crude or unadulterated forms have an essential role in pharmaceuticals. The research in medicines has been redirected to unmanageable disorders and chronic diseases like cancer and metabolic syndrome, while the diseases of the current era are still challenging for the field of medical science. Sequentially to acquire novel synthetic molecules, people have ignored the ancient and traditional remedies. Although man-made medicines provide quick relief from the diseases, their hazardous adverse reactions and effects on vital body organs, principally nephrotoxicity, hepatotoxicity and sometimes mortality, cannot be overlooked. Natural medicinal products are a blessing to humans from nature to promote healthy living devoid of any disease. People of prehistoric times had extended expectancies of life contrasted with the people of the current era. This was merely because the ancient

healthy lifestyle was absolutely dependent upon nature since ancient people used to take more traditional plants consisting of antioxidants and secondary metabolites in greater quantities. Previous research and documents proposed that chemical constituents in vegetables, fruits and herbs prevent oxidative injuries because of ROS and free radicals; moreover, they inhibit the risk of developing diseases.

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Chapter 13

Honey and Its Immunostimulatory Activities

Introduction

Honey is the organic product synthesised from flower nectar by *Apis mellifera* (honey bees) (Dashora, 2011). Humans have consumed honey since prehistoric times, around 5,500 years back. Several ancient peoples, including Babylonians, Greeks, Romans, Chinese, Mayans and Egyptians, used honey for its therapeutic properties and nutritional purposes (Samarghandian et al., 2017). Honey is a unique, bee-obtained natural product, and it has medicinal, nutritional, industrial and cosmetic values (Bansal et al., 2005; Samarghandian et al., 2017). Honey is evaluated as a well-balanced edible and is equally popular with females and males of all ages (Bell, 2007).

Natural therapeutic products have been consumed for thousands of years to manage several diseases. Though typical pharmaceutical approaches have replaced many, the extensive population has recently observed the revival of interest in the consumption of honey and its products. Apitherapy is the branch of alternative therapeutics that deals with the usage of bee products, i.e. royal jelly, propolis, honey, pollen and bee venom, to prevent and manage diseases (Ghosh & Playford, 2003). There are fundamentally two principal categories of honey, forest and apiary honey. The honey can be multifloral or monofloral, depending on whether the honey is assembled from the nectar of a similar blossom or the flower nectar of different types. The honey synthesised by the *Apis mellifera* and *Apis cerana indica* honey bees in apiaries and gathered by contemporary extraction methods is known as apiary honey, devoid of any foreign matter and transparent. Contrastingly, that synthesised in forests by *Apis dorsata* or from untamed nests of *Apis cerana indica* and assembled by the crude compressing comb method is recognised as forest honey. This kind of honey is cloudy or thick with suspended particles including plenty of bee larvae, wax, pollen, fragments of bees and other substances from plants. Hence,

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it is compulsory to filter the extracted honey to segregate the suspended materials (Subrahmanyam, 2007).

Initially, bees transform the nectar of flower to honey by regurgitation and vaporisation, then stock it as a fundamental source of food in honeycombs of wax under the beehive, with the amber golden transparent colour. Flavours of honey differ and are based on the categories of the flower by which the nectar was obtained. Subsequently, honey can be gathered from the hives for intake by humans. Honey is recognised as a source of medicine and food by both ancient and modern generations, cultures and traditions (Allsop & Miller, 1996; Crane, 1999; Crane & Bee Research Association, 1975; Jones, 2009).

In accordance with the Holy Bible, King Soloman asked to consume honey since it is healthful. Moreover, according to the Holy Bible, John the Baptist relished a diet consisting of untamed honey when he was moving in the wilderness or during a period of time when he was in the region of the desert. While Islam advised consuming honey, there is a separate Surah (chapter) in the Holy Quran, 'Surah Nahl', discussing honey bees and honey. In Buddhism, honey is believed to be among five essential foods and medicines. Other groups who had an interest in the use of honey as a food and medicine include Hindus and Jews. Honey is synthesised and distributed in significant quantities globally. Every year the USA celebrates the national month of honey during September as a promotional event, and this event aims to encourage honey as an organic and useful sweetener and for maintaining the bee industries of America (Allsop & Miller, 1996; Arawwawala & Hewageegana, 2017; Jones, 2009) (Figure 13.1).

Traditional Uses of Honey

The evidence from Paleolithic paintings demonstrates the management of ailments with bee products, for instance, the use of honey initiated 8,000 years ago. Antique tablets, scrolls, Sumerian clay tablets and books, Hindu scriptures (Veda), the Ebers papyri, the Holy Bible, the Holy Quran and Hippocrates elucidated that honey has been consumed extensively as a medicine (Mijanur Rahman et al., 2014; Molan, 2001; Samarghandian et al., 2017). The Quran strongly demonstrated the activity of honey's medicinal values (Bergman et al., 1983). God has encouraged the bees to construct their beehives on trees, in hills and in the habitations of humans; from inside their bodies emerges a liquid of different colours, in which there is a cure for mankind; certainly, this is an indication for those who believe (Samarghandian et al., 2017).

More than 4,000 years ago, honey was consumed as a traditional medicine in Ayurveda, where it was believed to be efficacious in harmonising all three *doshas* (humours) of the body. The prehistoric civilisation of Veda contemplated honey as one of the most exceptional gifts of nature for humankind. In Egyptian prehistoric times, honey was applied locally to manage wounds (Arawwawala & Hewageegana, 2017). Honey is identified as *kshaudra* or *madhu* in the scriptures of Ayurveda and is one of the most significant remedies utilised in Ayurvedic medicine. The earliest Greeks thought that intake of honey could assist in enhancing lifespan. Contemporary research study shows honey does have distinctive therapeutic and nutritional properties. Lots of studies have been published regarding honey, and many among them have emphasised biochemical examination, dietary and non-dietary commercial

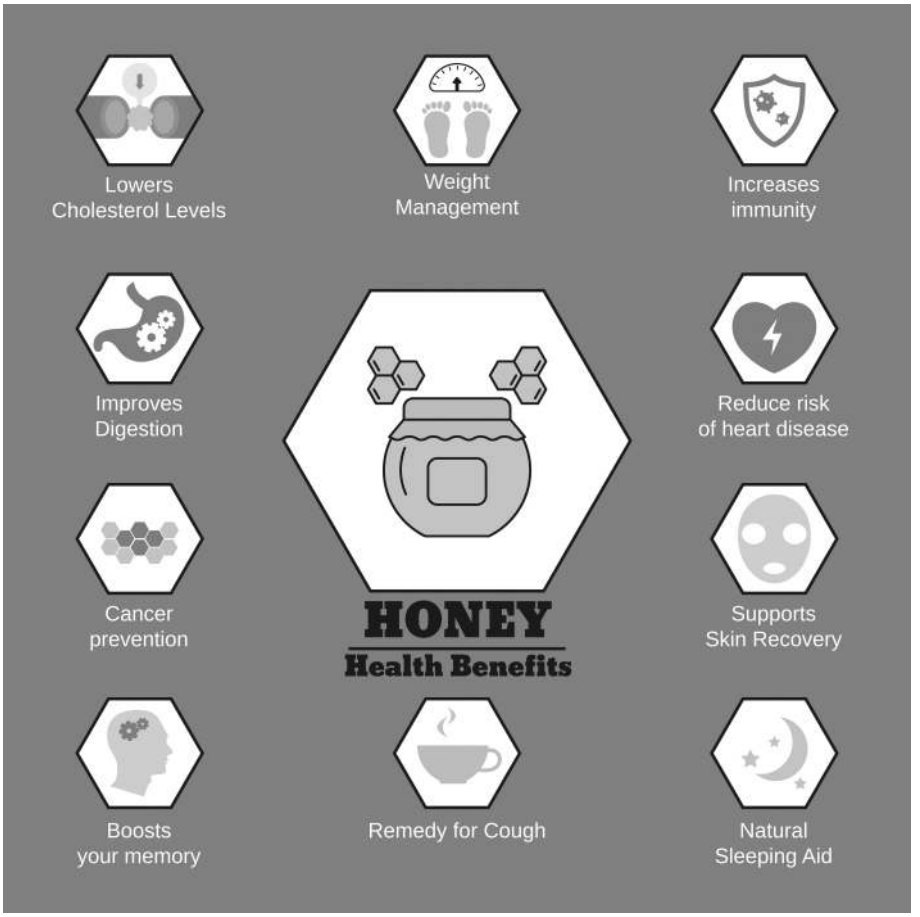

Figure 13.1 Health benefits of honey.

usage. Honey was consumed for a range of ailments including asthma, tuberculosis, dizziness, ophthalmic disorders, constipation, eczema, wound healing, hiccups, throat infections, thirst, piles, fatigue, hepatitis and infestation of worms in the traditional medicinal system (Arawwawala & Hewageegana, 2017; Bhishagratna, 2018).

Honey in Ayurveda Medicinal System

Honey is classified into various forms in Ayurveda. According to *Sushruta Samhita* (the ancient Sanskrit text of medicine and surgery), there are eight various forms of honey (Bhishagratna, 2018). (1) *Pauttika* honey has dry and hot properties leading to the vitiation of blood, *pitta* and *vata dosha*. (2) *Bhramara* honey means extremely heavy; it is difficult to digest and has a sweet taste. (3) *Kshaudra* honey is a light type of honey, which indicates it digests quickly. It has antiobesity effects and cooling properties. (4) *Makshika* honey is efficacious like all the previously mentioned types of honey and is extremely beneficial in managing dyspnoea and asthma.

(5) *Chhatram* honey is also heavy but is cooling. It is beneficial in the management of haemoptysis and infestations of worms. (6) *Arghyam* honey is astringent and has a pungent taste after digestion; it is extremely beneficial for the eyes. It greatly suppresses *kapha* and *pitta doshas* (body humours) compared to other kinds of honey. (7) *Auddalakam* honey has antitoxic properties and is beneficial in skin disorders; it also helps in improving the voice. (8) *Dala* honey is dry and useful in managing vomiting and diabetes.

There are two kinds of honey in Ayurveda according to the properties recognised as *purana madhu* (old honey) and *navina madhu* (fresh honey). Though *navina madhu* or fresh honey provides nourishment, it works as a mild laxative and enhances body weight. In contrast, *purana madhu* or old honey (nearly after one year of gathering honey) is drier than fresh honey, decreases fat and works as a fine adsorbent (Arawwawala & Hewageegana, 2017; Bhishagratna, 2018).

Use of Honey in Greco-Arabic and Islamic Medicine

Oenomel is an ancient Greek drink comprised of grape juice (unfermented) and honey. It is occasionally consumed as a traditional remedy for specific disorders of the nervous system and gout (Eteraf-Oskouei & Najafi, 2013). Hippocrates suggested an uncomplicated diet, and encouraged the use of honey as oxymel (honey and vinegar) for managing pain, hydromel (honey and water) for managing acute fevers and thirst, along with a blend of several therapeutic substances (Zumla & Lulat, 1989). Hippocrates also used honey for sore throat, prevention and management of scars, wound healing, constipation, ophthalmic disorders, sepsis, cough and as an antiseptic (Eteraf-Oskouei & Najafi, 2013). In Prophetic medicine, honey is contemplated as a healthy food item. The Holy Quran intensely elucidates the strong medicinal value of honey as honey was also advised by the Prophet Mohammad (PBUH) for the management of ailments (Molan, 1999). Nearly 1,000 years ago, Avicenna, a famous physician and scientist, suggested honey as one of the greatest tuberculosis treatments (Asadi-Pooya et al., 2003).

Composition of Honey

Currently, around 300 forms of honey have been identified (Lay-Flurrie, 2008). These types are associated with the various kinds of nectar that are gathered by the honey bees. Though these different varieties of honey are from different manufacturer bees, the nutrients found in 100 grams of the generally used honey include around 65 to 73.1% carbohydrates which comprise sucrose (0.23 to 1.21%), maltose (1.8 to 2.7%), glucose (25.4 to 28.1%) and fructose (35.6 to 41.8%) while 17 to 18% is water, and other nutrients including minerals, vitamins, proteins and amino acids are 0.50 to 1% (Cianciosi et al., 2018). Honey demonstrates changed compositions related to climate, species of bee, geographical and botanical origin (Al-Hatamleh, Boer, et al., 2020). The tremendous therapeutic properties of honey are related to the antioxidant phenolic constituents that differ in all types of honey, naturally based on the floral honey derivation; phenolic constituents are secondary metabolites established in honey with various chemical configurations, including polyphenols (flavonoids) and phenolic acids. In spite of the changeability in the compositions of honey,

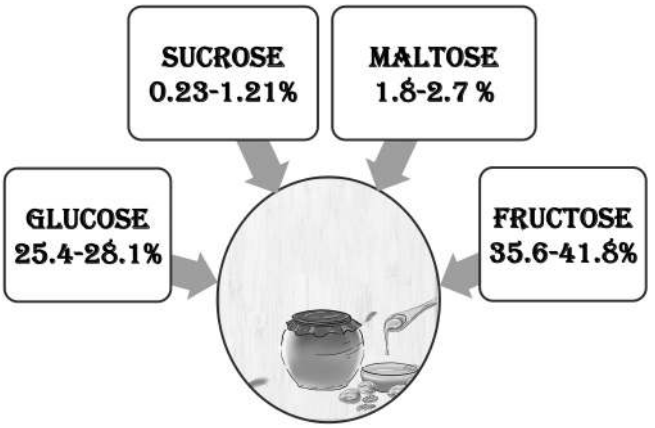

Figure 13.2 Percentage of carbohydrates in honey.

the most abundant flavonoids are genistein, kaempferol, luteolin, apigenin, galangin, pinocembrin, quercetin, chrysin and pinobanksin. However, the most plentiful phenolic acids are caffeic acid, syringic acid, gallic acid, vanillic acid, p-hydroxybenzoic acid, p-coumaric acid, syringic acid and chlorogenic acid (Cianciosi et al., 2018) (Figure 13.2).

Honey in pure form comprises polyphenols, flavonoids, glycosides, alkaloids, cardiac glycosides, volatile constituents and anthraquinone (Islam et al., 2012; White, 1980; White et al., 1962). Monosaccharides are the most significant sugars in honey and may be responsible for most of the nutritional properties and physical outcomes of honey (Manyi-Loh et al., 2011). Besides monosaccharides, minor quantities of disaccharides (laminaribiose, galactose, gentiobiose and sucrose), trisaccharides (isomaltose glucose, maltotriose, isopanose, melezitose and centose) and oligosaccharides are found in honey (Sato & Miyata, 2000; Siddiqui & Furgala, 1967).

Honey is classified as monofloral (from a single flower source) or multifloral (from different sources of flower). Lots of honey are monofloral, generally synthesised by bees of the genus *Apis*, and called after the related species of plant such as Manuka honey. Meanwhile, multifloral honey is produced by stingless bees (genus *Meliponinae*) (Jibril et al., 2019). It is yet uncertain which type of honey has better medicinal potential (Al-Hatamleh, Hatmal, et al., 2020).

Other Bee Products Used as a Source of Nutrients and Medicines

Propolis

One of the most significant constituents of bee products is propolis. It is primarily made up of 5% pollen, 10% essential oils, 30% wax, 50% resin and another 5% organic constituents (Gómez-Caravaca et al., 2006). Alcohols, terpenes, esters, steroids, aldehydes, flavonoids and phenolic constituents are the substantial organic

constituents found in propolis (Huang et al., 2014). Various flavonoids such as quercetin, myricetin, acacetin, pinocembrin, kaempferol, galangin, apigenin, chrysin, luteolin, catechin, naringenin and rutin, one derivative of stilbene named resveratrol and two phenolic acids (cinnamic acid and caffeic acid) have been identified in extracts of propolis by capillary electrophoresis (Volpi, 2004). Propolis also consists of essential vitamins such as vitamin C, vitamin E, vitamin B6, thiamine and riboflavin, and furthermore, beneficial minerals such as iron, potassium, magnesium, sodium, zinc, calcium, copper and manganese. Some enzymes, for instance, acid phosphatase, adenosine triphosphatase, glucose-6-phosphatase and succinic dehydrogenase are also found in propolis (Khalil, 2006). Propolis has been stated to have various biological activities, including anti-inflammatory, anticancer and antioxidant activities. There are some research projects that describe the medicinal use of propolis in the management of viral infections. One of the studies analysed the in vitro effect of alcoholic extract of propolis on the adherence and growth of trophozoites of *Giardia duodenalis* (Freitas et al., 2006). Another research study demonstrated that propolis has anti–*H. pylori*, anti-inflammatory, antihistaminergic and antacid activities that can be utilised to manage gastric ulcers (Paulino et al., 2015) (Figure 13.3).

Royal Jelly

Royal jelly is utilised in the feasting of queen bees and larvae as an exceptional nutrient, which is released from the mandibular and hypopharyngeal glands of worker bees (Matsuoka et al., 2012; Strant et al., 2019). Royal jelly is one of the bee products having a somewhat complicated structure. In its constitution, elements that target numerous identified and unidentified biological mechanisms play a significant role in the biomedical outcome of the royal jelly (Stocker et al., 2005). Royal jelly is enriched with vitamins, proteins, hormones, minerals, sugars and fatty acids needed for the evolution of the larvae. It comprises lipids (3–6%), minerals (3–8%), carbohydrates

Figure 13.3 Bee propolis along with honey.

(9–18%), protein (18%), water (60–70%), salt and vitamins; it also consists of various bioactive compounds that have immunity-boosting properties, such as peptides and 10-HDA (10-hydroxy-2-decenoic acid) (Margaoan et al., 2017; Premratanachai & Chanchao, 2014; Strant et al., 2019). An RCT study has stated that royal jelly is found to be beneficial in decreasing the symptoms of premenstrual syndrome (Taavoni et al., 2014). Another randomised controlled clinical study described the efficacy of royal jelly in the management of problems of the urinary tract and for enhancing the quality of life in postmenopausal women (Seyyedi et al., 2016).

It is beneficial for metabolism, production and regeneration of body cells, resulting in health, vigour, energy, great immunity and vitality of all tissues. The royal jelly is loaded with natural amino acids, acetylcholine, hormones, sterols, vitamins, phosphorus and EFAs (essential fatty acids). Acetylcholine is efficacious in the transference of nerve messages and for normal endocrine functioning. Royal jelly is also loaded with nucleic acids, which are the fundamental matter of life, and has anti-ageing outcomes since it also consists of gelatinous amino acid, the primary collagen constituent. Royal jelly has a gammaglobulin in its structure that helps in boosting the immune system and combatting infection. The constituent 10-hydroxy-2-decanoic acid has potent anti-infective activity against several fungi and bacteria. It is well recognised that royal jelly has been utilised successfully in neurology, tissue repair of cartilage and bones, urology, oncology, infertility, geriatrics, psychiatry, vascular stiffness and skin protection. It also has antimetastatic and antitumour effects. It has been reported that intake of royal jelly has a considerable impact on motility and count of sperm. Moreover, positive outcomes are acquired in the management of infertility (Ahmadnia et al., 2015; Strant et al., 2019) (Figure 13.4).

Pharmacological Uses of Honey

Antibacterial Effects of Honey

The antimicrobial effects of honey are one of the most substantial discoveries that were initially identified in 1892 by Van Ketel (a Dutch scientist) (Eteraf-Oskouei & Najafi, 2013). The current study specifies that the efficacy of honey in a number of its therapeutic uses is because of its antimicrobial activity that is capable of reducing gram-negative and gram-positive microbes, including multiple drug-resistant microbial strains (Kwakman et al., 2008), and a few species of viruses and fungi

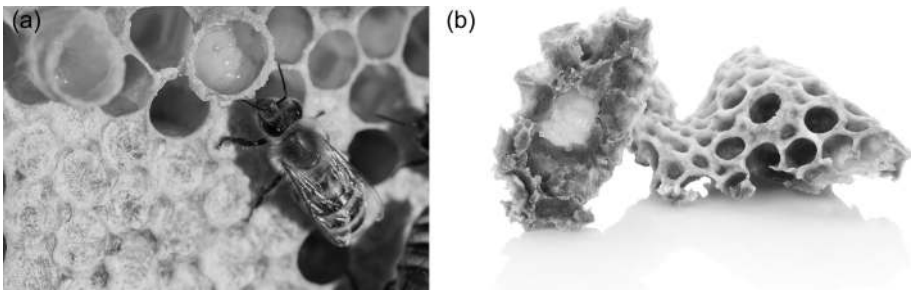

Figure 13.4 Royal jelly in the honeycomb.

(Scepankova et al., 2017). Junie et al. (2016) contrasted in vitro antimicrobial activity of different categories of honey from various sources against the microbial resistant strain separated from patients, including *Listeria monocytegenes*, *Salmonella enterica serovar Typhimurium*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Bacillus cereus*, *Staphylococcus epidermidis*, *Bacillus subtilis* and *Escherichia coli*. The outcomes demonstrated that all of the honey samples showed antimicrobial activity against the researched strains of microbes and that all the samples reduced the growth of microbes (Junie et al., 2016). The verifications were identical to other research studies carried out elsewhere. It has been clearly expressed that honey holds a considerable antimicrobial activity against a number of bacteria that have already developed resistance to antibiotics (Junie et al., 2016; Scepankova et al., 2017).

In research carried out by Wasihun and Kasa (2016), the antimicrobial activity of honey was analysed against drug-resistant strains of human pathogenic microbial isolates, i.e. *Klebsiella pneumonia*, *Escherichia coli*, *Proteus mirabilis*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa* and coagulase-negative *Staphylococcus* (Wasihun & Kasa, 2016).

The values of minimum bactericidal concentration and minimum inhibitory concentrations specified that the experimented honey had potent bacterial-killing and bacteriostatic activities against the experimented microbes. Unlike several antibiotics, doses of honey may not cause resistance in microbes, and it may be consumed persistently (Eteraf-Oskouei & Najafi, 2013). However, the microbial killing rates for Manuka and Sidr honey were substantially greater than those observed with the solitary antibiotics. Hence, the consumption of honey in a medical setup is contemplated to be beneficial in fighting microbial resistance (Kwakman et al., 2008). Despite this, there are therapeutic grade honey such as Manuka honey and Revanil source honey. Possessing consistent antimicrobial activity, these honey are synthesised in under-regulated situations in greenhouses and every batch is studied separately to analyse UMF (unique Manuka factor) that provides a figure depending on its antimicrobial activity (Scepankova et al., 2017).

Immunomodulatory Effects of Honey

A group of researchers reported that two of the honey from New Zealand, i.e. pasture and Manuka honey, considerably decreased the synthesis of ROIs (reactive oxygen intermediates) by a cellular line of monocytes (i.e. MM6). Pasture honey was established to be extremely effective honey. The investigators also showed that pasture and Manuka honey activated the synthesis of TNF-α by similar cells (Tonks et al., 2001).

The exact mechanism of action behind immunostimulatory activities of honey was unidentified; however, the authors proposed that increased hydrogen peroxide levels in the pasture honey may have persuaded negative feedback consequences on the synthesis of reactive oxygen intermediates by the monocytic cell lines (MM6). ROS are produced in ample amounts in chronic wounds and trigger inflammation (Wlaschek & Scharffetter-Kochanek, 2005). Hence honey could be used in the management of chronic wounds because of its inflammation-suppressing properties by means of reducing the synthesis of reactive oxygen intermediates.

It was then inferred that pasture and Manuka honey have immuno-stimulatory activities and that these detections may at least partly describe the perceived

outcomes of honey in healing of wounds, especially as tumour necrosis factor-α has been demonstrated to encourage activation of macrophages, invigorate re-epithelialisation and angiogenesis in the duration of primary wound healing (Barrientos et al., 2008).

Furthermore, Tonks et al. (2003) stated that pasture and Manuka honey of New Zealand and jelly bush honey of Australia encouraged the enhanced synthesis of cytokines interleukin-6, tumour necrosis factor-α and interleukin-1β by human monocytic cell lines (MM6) and blood monocytes. Jelly bush honey from Australia was established to be most productive with peak levels of cytokine ranging from 0–500 pg/ml for tumour necrosis factor-α, 0–120 pg/ml for interleukin-1 beta and 0–1300 pg/ml for interleukin-6. The constituents in honey that invigorated the up-regulation of cytokine synthesis were not recognised. Since the cytokines estimated in the research are expected to play their part in the healing of wounds, for instance, interleukin-6 has been demonstrated to increase the multiplication of keratinocytes, and moreover, to attract IL-1β and neutrophils which encourages the secretion of significant growth factors for healing of wounds. The researchers proposed that this immunostimulatory outcome may describe the wound-managing properties of honey (Barrientos et al., 2008).

Role of Honey in Respiratory Ailments

Honey is a well-recognised therapy for symptoms of upper respiratory tract infection. Guidelines advised honey in children for acute cough. Honey probably alleviates the symptoms of upper respiratory tract infections, with the powerful manifestation in the context of severity and frequency of cough. Lots of verifications encourage its consumption in preference over regular care for other symptoms of upper respiratory tract infections, and lots of verifications emerge from research studies among children. Honey is a regularly consumed remedy that is well identified by patients. Honey is less harmful and more efficient in contrast with usual alternative care, and it doesn't cause any microbial resistance (Abuelgasim et al., 2021).

Honey as Cicatrisant

A wide range of wounds is being managed all around the globe with unadulterated natural honey from various sources. Medihoney™ (a mixture of jelly bush and Manuka honey) has been one of the initial therapeutically certified honey, authorised as a medicinal product and healing agent for professional management of wounds in Australia, Europe and America. Moreover, the dressings soaked and saturated with honey in regulated situations and sterilised or disinfected by γ-irradiation are accessible in New Zealand and Australia. Honey is similarly established as an active constituent in products, for instance, ointments to manage cuts and minor burns in Nigeria (Loh et al., 2011).

Honey is a cost-effective and efficient therapy for the management of diabetic foot ulcer, which is frequently complicated by bacterial infections that decelerate the process of healing. Besides the infection, clinical indications, for instance, redness, pain and swelling, might not be found because of the peripheral neuropathy in diabetic subjects and due to the decreased response from the immune system, which

further makes the diagnosis more difficult. One of the review studies specified that applying honey for the management of venous ulcers provided positive results with fine rates of acceptance from the patients. Honey is utilised for wound healing and is found to be effective in patients with topically infected wounds, Charcot foot ulcerations, diabetic foot ulcers and complicated disease conditions that have absolutely ceased to respond to hospital treatments. Moreover, there is remarkable tolerability and least injury to the wound bed in the use of honey (Dunford & Hanano, 2004; Pasupuleti et al., 2017).

Anti-Inflammatory Effects of Honey

The anti-inflammatory activity of honey is principally associated with its antiseptic properties that function by eliminating infection-causing microbes, invigorating the inflammatory reaction and decreasing the number of bacteria established in the wound (Hadagali & Chua, 2014). In point of fact, honey can eliminate microbes that initiate inflammation; a reduction in inflammation of wounds after applying a gauze of honey has been related to its uninterrupted anti-inflammatory properties, for instance, antioxidant activity (Yaghoobi et al., 2013). Particularly, a number of antioxidant phenolic constituents, i.e. flavonoids, are greatly associated with its anti-inflammatory activities, as formerly stated in the literature. The anti-inflammatory properties of honey have been related to synergetic outcomes of the phenolic constituents found in honey, including caffeic acid and kaempferol (Scepankova et al., 2017).

Apart from wound inflammation (Tomblin et al., 2014), the association between honey's antioxidant capability and its anti-inflammatory activity has been perceived in other models of inflammation as well (Owoyele et al., 2011). Manuka honey has been demonstrated to precisely diminish the inflammatory reaction related to ulcerative colitis distinguished by an over-expression of inflammatory cells, perhaps by enhancing antioxidant activity (Scepankova et al., 2017). In research conducted by Borsato et al., extract of honey reduced infiltration of white blood cells, reduced oedema and diminished the synthesis of reactive oxygen species during the process of inflammation chemically persuaded in mice ears (Borsato et al., 2014).

Generally, NF-KB (the transcription factor) plays a chief role in developing inflammation, being identified as an indicator of inflammation (Vallianou, 2014). The anti-inflammatory activity of honey has been noticed in several reports, mentioning that honey can reduce the secretion of proinflammatory cytokines, synthesis of reactive oxygen species and appearance of nitric oxide synthase, and also inhibits the levels of prostaglandins, one of the vital players in the inflammatory process (Scepankova et al., 2017). One of the in vivo studies conducted by Owoyele et al. (2011) mentioned that honey caused a reduction in the secretion of nitric oxide in chronic and acute inflammation. Moreover, Gelam honey has been researched in a model system of acute inflammation, demonstrating oedema inhibition in rodents' inflamed paws. The mechanism was related to reducing inducible nitric oxide synthase and cyclooxygenase, ultimately resulting in subdued levels of proinflammatory mediators such as interleukin-6, nitric oxide, tumour necrosis factor-α and PGE2 (Hussein et al., 2012). Usually, the primary reaction of the body towards any harmful stimuli is acute inflammation, and the number of reactions is distinguished by pains (Hadagali & Chua, 2014). It has been demonstrated that honey considerably inhibited the synthesis of proinflammatory cytokines, which was identical to

the outcome of the indomethacin (anti-inflammatory drug), and also could regulate muscarinic receptors to create its analgesic effect, hence possibly being beneficial for the management of inflammation (Scepankova et al., 2017).

Honey in Skin Disorders

Honey has traditionally been consumed and applied to manage skin ailments with either immunological or microbiological causes. In Ayurveda, for instance, honey is applied to manage wounds, burns, eczema, cuts, Fournier gangrene and dermatitis (Ediriweera & Premarathna, 2012; McLoone et al., 2016). In contemporary clinical practice, Manuka honey, which is synthesised by *Apis mellifera* (honey bees), is smeared locally in the management of wounds (Irish et al., 2011). Honey has been endorsed for clinical application in various regions, including the USA, New Zealand, the UK, Canada and Australia. A considerable population of the world suffers from dermatological ailments, and these can have a significant influence on quality of life (Mahler et al., 2009). Disorders of skin have been demonstrated to have a range of causes; lots of them are related to bacterial invasion of the skin, others with irritants exposure, for instance, cosmetics chemicals, while others may be caused by hypersensitivity reactions to allergens (Fonacier et al., 2010). Additionally, in vitro research has proposed that a variety of honey that originated from flora can harmonise the skin's immune system; both anti-inflammatory and immunity-boosting outcomes have been noted (Majtan et al., 2009, 2013).

Anticarcinogenic Effects of Honey

Recent studies demonstrate that honey may provide anticarcinogenic activities by means of numerous mechanisms. Systematic examinations have stipulated that honey has anticancer effects via its intervention with numerous pathways of cell signalling, including antimutagenic, anti-inflammatory, apoptosis and antiproliferative pathways. Honey also alters the responses of the immune system (Eddy et al., 2008) and has been shown to encourage the death of cancer cells, alter the progression of the cell cycle, prevent the multiplication of cancer cells and originate depolarisation of mitochondrial membrane in different kinds of carcinoma such as cervical cancer, adenocarcinoma of epithelial cells (Erejuwa et al., 2014), melanoma (Pichichero et al., 2010), prostate cancer, lung cancer and renal cancer cells (Samarghandian et al., 2010, 2011, 2014), endometrial carcinoma cells, human NSCLC (non-small cell lung cancer), bladder carcinoma, carcinoma of the kidney (Samarghandian et al., 2017), leukaemia, osteosarcoma and oral squamous cell carcinoma (SCC) (Ghashm et al., 2010). Additionally, honey could be capable of decreasing different forms of tumours in animals, including melanoma, colon, breast, bladder and hepatic carcinoma. However, further research projects are required to enhance the understanding of the beneficial outcomes of honey in cancer (Samarghandian et al., 2017).

Role of Honey in Gastrointestinal Disorders

Honey is stated to have an impact on the prevention and management of GI ailments, including gastroenteritis, gastritis and peptic ulcer disease (PUD). Honey

is a powerful inhibitor of *H. pylori*, the causative agent of gastritis and peptic ulcers (Osato et al., 1999). Honey is obtained from a natural source and does not enhance blood glucose levels; a blend of water with honey is a wonderful remedy for colic (Mann & Truswell, 2017). The prebiotic effects of honey enhance the growth and quantity of healthy gut microflora that are essential for maintaining the health of the GI tract. In accordance with Kajiwara et al, the intake of honey enhances the growth of bifidobacterium, while its compounds were established to produce prebiotic effects that hold resemblance with the effects of FOS (fructooligosaccharides) (Kajiwara et al., 2002). Numerous groups of researchers have confirmed the traditional assertions about honey by means of research-based controlled trials. Honey is consumed to manage and prevent gastrointestinal tract infections, i.e. duodenitis, gastritis and gastric ulceration originated by microbes and viruses (for instance, rotavirus) (al Somal et al., 1994; Haffejee & Moosa, 1985; Tallett et al., 1977).

Antiviral Effects of Honey

A number of bioactive constituents in honey have demonstrated potent antiviral activities (i.e. hesperidin, chrysin, galangin, methylglyoxal and caffeic acid) or increasing antiviral immune reactions. Previous studies on patients suffering from HIV demonstrated that intake of honey aids to enhance their immunity by means of the rise in the proliferation of lymphocytes, and in general, makes the biochemical and haematological status better (e.g. platelets, erythrocytes, copper, haemoglobin, levels of proteins and neutrophils) (Al-Hatamleh et al., 2020; Al-Waili et al., 2006).

Honey is demonstrated to be efficient for using topically to manage recurrent skin disorders caused by the herpes simplex virus (Al-Waili, 2004). Moreover, clover and Manuka honey have in vitro antiviral effect that has been documented against the varicella-zoster virus (Shahzad & Cohrs, 2012). Another study has revealed that honey, including Renge, soba, Manuka and acacia, have antiviral activities, and Manuka honey is the most powerful antiviral agent against influenza virus (H1N1) in the MDCK (Madin-Darby canine kidney) cultured cell line (Watanabe et al., 2014). Honey also have the ability to foster proinflammatory cytokines such as interleukin-6, tumour necrosis factor and interleukin-1 related to the systemic effects of COVID-19 infection (Mangalmurti & Hunter, 2020); taking honey might assist in decreasing the COVID-19 severity either by its strong antiviral effects against SARS-CoV-2 or by means of boosting the immune system (Al-Hatamleh et al., 2020).

Conclusion

Honey has been reintroduced in the recent era as an age-old medicine. It is composed of various constituents that can provide health and nutritional benefits. Its medicinal potential has been ascribed to its antimicrobial, antioxidant, anti-inflammatory, wound healing and immunity-boosting properties. Furthermore, honey's effectiveness against drug-resistant and drug-sensitive infectious agents, ease of application in the management of wounds, lack of adverse effects in relieving stomach pain, lessening the duration of diarrhoea and other health benefits all add up to the fact that honey could be a viable alternative way of chemotherapy and/or chemoprophylaxis. The physiological effects of honey's distinctive oligosaccharide constituents

and antimicrobial processes are of great interest to researchers. However, a more thorough examination of honey's possible prebiotic impact on probiotic bifidobacteria and lactobacilli, as well as on the mechanisms of action involved, may be required before the functional component can be used to generate scientifically supported health claims.

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Chapter 14

Therapeutic Potential of *Nigella sativa* (Black Seed)

Introduction

Nigella sativa is typically recognised by the names of black cumin, *kalonji*, *habbatus sauda* and black seed; its countless nutritional and medicinal values commonly distinguish it from other herbs. Black seed has numerous nutrients, including vitamins, minerals and other phytoconstituents, especially thymol, carvacrol and thymoquinone, which has remarkable medicinal properties. The seed extract of *Nigella sativa* is stated to have a range of therapeutic properties, including anti-inflammatory, anticancer, antidiabetic, anti-infectious and immunity-boosting effects. The plant *Nigella sativa* belongs to the *Ranunculaceae* family and is considered one of the substantial medicinal plants in history; it has been advised for thousands of years, and it also has religious importance because it is mentioned in the holy books of different religions. The latest various research and scientific studies have validated all the traditional claims about black cumin (Gilani et al., 2004; Tavakkoli et al., 2017).

The seeds of *Nigella sativa* are consumed in the different traditional medicinal systems for the management of ailments including cough, asthma, bronchitis, inflammation, fever, lumbago, chest congestion, paralysis, infertility, flatulence, headache, dizziness, dysentery and dyspepsia (Dunlop, 1968; Durmuşkahya & Ozturk, 2013; Gholamnezhad et al., 2016; Nasir et al., 2014); moreover, black seed oil is consumed as the cure for the inflammation of joints, eczema, inflammation of testes and abscess. Black seed oil is also used to blend with honey for complaints of asthma, chest congestion and bronchospasm (Gholamnezhad et al., 2016; Nasir et al., 2014). Black seed is also ascribed as a diuretic, digestive, appetiser, analgesic and hepatic tonic in the earliest pieces of literature. It consists of more than 2,000 identified species of blooming plants in 43 subdivisions, which are disseminated all around the globe. The most remarkable genus is Ranunculus which consists of 600 species that also incorporate *Nigella sativa* (Ahmad et al., 2021) (Figure 14.1).

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Figure 14.1 *Nigella sativa* (black seed).

The extensive historical and religious background of black seed usage is mentioned in different pieces of literature. It is stated in the antique testimony of the Bible and is established in the book of Isaiah, where it is mentioned as 'ketzah', a seasoning for cake and bread that can be consumed in numerous ways (Naz, 2011). The names *gith* and *melanthoin* refer to black seed in ancient literature (Rahmani & Aly, 2015); it is also referred to in traditional Indian and Chinese medicine. It has been utilised to manage numerous ailments for centuries and is recognised as an essential medicine in the Indian medicinal system. Black seed has also been reviewed in the Islamic and Greco-Arabic medicine by the name of 'Habb e sauda'; it is recognised as prophetic or *sunnah* medicine because the Prophet Muhammad PBUH has consumed it. Moreover, it is also mentioned in *Sahih al Bukhari* as a remedy for all diseases except death (Buk̲ ārī et al., 1994).

Various researchers have experimented and recorded the dosage forms and administration of black seed constituents analysed in inflammation and nociception models. *Nigella sativa* has been a significant research focus and has lots of traditional utilisation. Hence it has been broadly researched for its biological effects and chemical compounds. Furthermore, it is worth stating that black seed has antimicrobial activity against MRSA (methicillin-resistant *Staphylococcus aureus*) (Hannan et al., 2008), antiseizure effects (Akhondian et al., 2011), antidiabetic effects (Mathur et al., 2011), as well as immunostimulatory activities enhancing the NK cells' and T cells' immune reactions (Salem, 2005). Numerous animal studies have discovered the different activities of black seed oil in various aspects of the metabolic syndrome, such as low-density lipoprotein, total cholesterol, BP and blood sugar. Moreover, lots of them have stated the beneficial effects of black seed in metabolic syndrome. However, further exploration is needed to find out the mechanisms by which black seeds act on different aspects of diseases (Najmi et al., 2008).

This chapter will discuss the historical and religious importance of black seed, its nutritional values and phytochemical constituents, especially thymoquinone, and the pharmacological activities of *Nigella sativa*.

Historical and Religious Importance of Black Seed

Historical use of this wonderful herb started with the ancient Greeks, Egyptians and Romans. *Nigella sativa* and their phytoconstituents have treated numerous ailments for millennia and have a considerable place in traditional Chinese medicine. *Nigella sativa* is also contemplated as an essential medicine in the Indian system of medicine for preventing a range of diseases and for its ability to manage gynaecological disorders, anorexia nervosa and nervous system disorders. In many Asian, Arabian and African countries, *Nigella sativa* oil is a natural source of remedies for numerous ailments, including several allergies (Rahmani & Aly, 2015). Both oil and seeds are drawn out from the *Nigella sativa* plant and are used medicinally (Khan et al., 2011). Unani or Greco-Arabic medicine is significantly based on the practices and beliefs of Ibn Sina or Avicenna and, in his book, the *Canon of Medicine* (which was considered the most famous and authentic source of knowledge not only in the Islamic world but also in other parts of the world), Avicenna favoured and advised the use of black seed as an energising herb for the body and as a healing agent for headache, fever, common cold and toothache (Amin & Hosseinzadeh, 2016).

Black seed was also suggested as a pacifying and soothing agent for wounds, skin irritations and other skin ailments. In the traditional system of medicine, the black seed and its oil have been prescribed more often as a natural management for various disorders like cough, dyspnoea, fever, diabetes, asthma, hypertension, nasal congestion, inflammation, dizziness, bronchitis, eczema and gastrointestinal issues. It is also advised in pain conditions such as back pain, headache and toothache (Tariq, 2008). In Arabian and other Gulf countries, *Nigella sativa* is suggested for a broad range of ailments, including migraine, obesity, dysmenorrhea, inflammation, pain, hypertension, respiratory ailments, paralysis, infections, hemiplegia, fever, dysentery, flatulence, rheumatism, weakness of immune system and dyspepsia. The *Nigella sativa* seed extracts are utilised by Greco-Arabic (Unani) physicians, i.e. *tabibs* or *hakims* and *vaids* in Ayurvedic medicine, to manage numerous medical ailments, including obesity, HTN and dyslipidemia (Qidwai et al., 2009). Black seed has also been consumed as a carminative, stimulant, antifungal, lactagogue, antimicrobial, emmenagogue, diuretic and anthelmintic it has also been applied topically in orchitis, abscesses, ulcers, swollen joints and eczema (Tariq, 2008).

Nutritional Values and Phytochemical Constituents of *Nigella sativa*

To date, numerous chemical constituents have been drawn out and recognised from various species of black seed (Ahmad et al., 2013). The black seed consists of 406 grams of fat, 216 grams of protein, 249 grams of free nitrogen extract, 84 grams of fibre, 45 grams of ash, 38 grams of moisture, 1,860 mg of calcium, 105 mg of iron, 527 mg of phosphorus, 60 mg of zinc, 18 mg of copper, 57 mg of niacin, 15.4 mg of thiamine and 160 micrograms of folic acid per kilogram. Further research has revealed the appearance of various active pharmaceutical constituents in the black seeds, including longifolene, thymol, carvacrol, T-anethole benzene, 4-terpineol, α-pinene, thymoquinone, p-Cymene and limonene (Toma et al., 2015). Some more research studies on plant chemicals have shown that the seed of *Nigella sativa* consists of two groups of alkaloids, including pyrazole alkaloids (nigellicine and nigellidine)

and isoquinoline alkaloids (nigellimine-N-oxide) (Kooti et al., 2016). Black seeds are also loaded with unsaturated fatty acids such as palmitic acid, linoleic acid and oleic acid (Kaskoos, 2011); other constituents of the seeds comprise cardiac glycosides, calcium, vitamins, saponins, flavonoids, alkaloids and minerals (Kooti et al., 2016).

Thymoquinone

It is the chief constituent of black seed volatile oil and has a diverse range of therapeutic properties such as antibacterial (Goel & Mishra, 2018), hepatoprotective (Hassanein et al., 2016; Laskar et al., 2016; Saheb et al., 2016), fungicidal (Almshawit & Macreadie, 2017), anti-inflammatory (Abd-Elbaset et al., 2017; Shaarani et al., 2017), antioxidant (Erol et al., 2017), anticancer (Majdalawieh et al., 2017; Shaarani et al., 2017) and nephroprotective activities (Kotb et al., 2018).

TQ is among the powerful active constituents of *Nigella*, as discussed before (Shanmugam, Ahn, et al., 2018; Shanmugam, Arfuso, et al., 2018; Siveen et al., 2014; Woo et al., 2012). It also showed anti-tumour activity against hepatic cancer cell lines in humans by increased activity of the caspase-3 enzyme, decreased contents of malondialdehyde, induced apoptosis of cells and impeded cellular growth (Ismail et al., 2018). This constituent has also been demonstrated to be a robust pharmacological adjuvant in cancer cell lines of human breast carcinoma, and in a few other cases, anticancer medicines along with TQ can manifest synergistic and antagonistic effects (Bashmil et al., 2018).

Pharmacological Activities of *Nigella sativa*

Numerous research trials have verified many effects of black seed and its derivatives, acquired in the previously mentioned in vivo and in vitro studies. Principally, in the available online database about research trials, there are several research-based studies on *Nigella sativa* including studies about obesity, blood cholesterols, diabetes, asthma and arsenical keratosis. The consumption of black seed was either alone or with one or any combination of herbs such as curcumin and with various dosages for up to two months. A few of the outcomes were positive, such as asthma and total cholesterol (Koshak et al., 2017; Qidwai et al., 2009). The clinical studies also revealed that black seed is effective in several skin disorders and has skin-protective effects.

Antioxidant Effects of Nigella sativa

Some research studies propose that black seed extracts and oils have antioxidant properties and can harmonise oxidative stress, hence it is beneficial in oxidative stress-associated disorders. Therefore the extracts and oils of black seed have proven in vitro (Abedi et al., 2017; Toma et al., 2015), in vivo (Mahmoudi et al., 2018; Rasoli et al., 2018) and ex vivo antioxidant activity (Salehi et al., 2021); furthermore, daily consumption of alcoholic extract of black seed decreased the peroxidation of lipids. It increased the catalase enzyme activity in rats (Rasoli et al., 2018). Another study proposed that hexane and hydroalcoholic extracts of black seed in addition to

thymoquinone may prevent oxidative stress caused by consuming high-fat-containing diets, e.g. the activity of total antioxidant capacity in serum and catalase enzyme is increased, whereas the levels of malondialdehyde are decreased (Mahmoudi et al., 2018). With regards to other species of *Nigella*, the alcoholic extract of *Nigella damascena* (70%) has demonstrated in vitro antioxidant properties generally even greater than the seeds of *Nigella sativa*; the former consisted of quercetin derivatives in more significant amounts. As discussed before, thymoquinone can have a defensive role in opposition to oxidative stress (Woo et al., 2013). In vitro antioxidant activities of thymoquinone have also been observed, particularly utilising the ORAC (oxygen radical absorbance capacity) (Tesarova et al., 2011); moreover, the essential oil drawn out from the seeds of *Nigella sativa* has excellent content of thymoquinone, and it demonstrated more powerful antioxidant properties than EOs of others (Abedi et al., 2017).

Anti-Inflammatory Effects of Black Seed

The anti-inflammatory effects of chief constituents and essential oil of *Nigella sativa* were assessed by estimating their ability to decrease nitric oxide production in cells. NO is produced from L-arginine in different tissues by the enzyme NOS (nitric oxide synthase) (Bourgou et al., 2010). The black seed essential oil's activity was analysed on macrophages RAW 264.7, which were encouraged to cause excessive production of nitric oxide. The black seed EO demonstrated a potent inhibitory activity on lipopolysaccharide-induced secretions of nitric oxide with $82 \pm 0.4\%$ reduction noticed at 25 μg/ml. TQ was identified as the highly active constituent, decreasing nitric oxide production at 25 μm by $90.21 \pm 0.2\%$. El-Mahmoudy et al. (2002) stated that thymoquinone arbitrates its reducing effect on nitric oxide synthesis by decreasing protein expressions and inducible nitric oxide synthase mRNA; hence, this constituent may be accountable for the anti-inflammatory effects of oil. Inhibition of NO was also revealed at 45 μm by α-thujene, thymol, α-pinene, p-cymene and γ-terpinene. The anti-inflammatory capability of black seed essential oil could be arbitrated, at least partly, by its direct powerful antioxidant effects as an efficient hunter of reactive oxygen species (Kazemi, 2014). It has been demonstrated that the nitric oxide synthase enzyme activity is consistent in carcinoma, and its critical regulation has been advised as a powerful chemoprevention strategy for reduction in the multiplication of cancer cells (Nishikawa et al., 2004). As a matter of fact, inflammatory arbitrators, i.e. nitric oxide, have been stated to give rise to mutagenesis (Marletta, 1993). The reduction of nitric oxide synthesis may be a favourable strategy for managing numerous inflammatory diseases. Black seed essential oil demonstrated antioxidant, antibacterial and anti-inflammatory activities and these outcomes favour the long-established use of this plant in inflammation, infections and pain (Kazemi, 2014).

Black Seed in Wound Healing and Management of Skin Disorders

The healing of wounds has extensively been the centre of attention in regenerative medicine, relatively because of the availability of the dermal tissues and their unconscious capability to regenerate (Gurtner & Chapman, 2016). Recently the stress of

managing and healing wounds has escalated along with the advent of multiple-drug-resistant microorganisms that can hinder the process of wound healing (Lai et al., 2017). Although skin can regenerate its damaged cells since a local defensive mechanism is instinctively turned on in the body, the appearance of certain inevitable situations, such as burns, chronic non-healing ulcers or unending wounds, could impede the healing process (Pereira & Bártolo, 2016). The constructive and beneficial effects of black seed in the healing of wounds are principally because of the angiogenesis elicitation, escalated proliferation of fibroblasts and successive collagen synthesis. *Nigella sativa* has also been stated to decrease tissue destruction, appearance of WBCs and microbial infections (Sallehuddin et al., 2020).

Antidiabetic Effects of the Black Seed

Diabetes mellitus prevalence is rising globally, and the patients with type 2 diabetes mellitus stated to be treated with the seeds of *Nigella sativa* in a dose of 2 grams per day for up to 12 weeks were found to have reduced after-meal blood glucose levels, the resistance of insulin, levels of fasting blood sugar and subsequently reduces the HbA1c. Black seed has also been revealed to increase the concentration of HDL significantly and help in reducing the concentration of low-density lipoproteins, triglycerides and total cholesterol (Bamosa et al., 2010). Some active constituents of black seed escalate the insulin secretions by making the energy metabolism of mitochondria better, simultaneously enhancing the intracellular activities of insulin receptors (Mansi, 2005).

Thymoquinone and other active antioxidant compounds of black seed escalate insulin secretions by means of enhancing the energy metabolism of mitochondria, simultaneously improving the intracellular pathways of insulin receptors (Mansi, 2005). Amid all mechanisms, the antioxidant processes are an important way to regulate high blood glucose in diabetic cases. Black seed increases the antioxidant enzymes, causes a reduction in oxidative stress and subsequently accelerates the regeneration of pancreatic β cells (Abdelmeguid et al., 2010; Houcher et al., 2007; Kanter, 2008; Sultan et al., 2014). Moreover, it enhances the quality of islet cells, decreases insulin resistance and escalates secretions of insulin (Bamosa et al., 2010; Mansi, 2005; Ahmad et al., 2021). Thymoquinone and black seed reduce the appearance of gluconeogenic enzymes such as glucose six phosphatase and also reduce gluconeogenesis, thus demonstrating considerable effects in regulating blood sugar levels, especially in patients with diabetes (Abdelmeguid et al., 2010; Houcher et al., 2007).

Antimicrobial Activities of Nigella sativa

Exploratory studies have shown that extracts of *Nigella sativa* have synergistic effects on the elimination of *Escherichia coli* along with antibiotic medicines, for instance, streptomycin, doxycycline, chloramphenicol, gentamycin, nalidixic acid, ampicillin, cephalexin and terbinafine (Morsi, 2000; Ara et al., 1970). Moreover, black seed has inhibitory effects on bacterial growth such as *Corynebacterium pseudotuberculosis*, *Staphylococcus aureus*, *Yersinia enterocolitica*, *Brucella abortus*, *Escherichia coli*, *Trueperella pyogenes*, *Listeria monocytogenes*, *Corynebacterium renale*, *Pasteurella multocida* and *Mannheimia haemolytica*. Another study has revealed that black seed

oil has an antistaphylococcal activity similar to that of antibiotics such as cefaclor, ceftazidime, cefamandole and cefuroxime (Kooti et al., 2016).

Antifungal Activities

The alcoholic extract of black seed demonstrates powerful antifungal activities. It shows inhibitory outcomes in rodents against candida infections. Moreover, in one of the studies, antidermatophyte effects of thymoquinone and black seed extract were evaluated against eight dermatophyte species: one species each of *Microsporum canis*, *Trichophyton mentagrophytes*, *Trichophyton interdigitale*, *Epidermophyton floccosum* and four species of *Trichophyton rubrum* (Bita et al., 2012; Kooti et al., 2016).

The extract of black seed reduces candida growth (Khan et al., 2003). Other antifungal effects of black seed extract were also seen in opposition to *Candida albicans*; it was stated that thymoquinone reduces in vitro *Fusarium solani* and *Aspergillus niger* activity identically to amphotericin-B (an antifungal medicine) (Ahmad et al., 2021; Aljabre et al., 2005). Average antifungal effects were established by thymoquinone in the three most important groups of dermatophytes *Microsporum*, *Epidermophyton* and *Trichophyton*. The other extracts of black seed also reveal antifungal outcomes; however, they produce more beneficial results in greater concentrations. The MIC of thymoquinone against a range of dermatophytes varies between 0.125 and 0.25 mg/ml (Ahmad et al., 2021; Aljabre et al., 2005).

Anticarcinogenic Effects of Nigella sativa

Black seed has antioxidant, antimutagenic, antiproliferative, cytotoxic, proapoptotic and antimetastatic effects, highlighted by numerous mechanisms (Majdalawieh & Fayyad, 2016). Various research studies about cancer cell lines, including epithelial, cervical, A-549 cells of lungs and MCF-7 breast cancer cells, have demonstrated that the administration of alcoholic black seed extracts, nanoemulsions and oil distinctly decreased the viability of cells, causing apoptotic cellular death, and/or changed the morphology of cell with values of IC50 between 0.41 and 82 µl/ml in few cases (Salehi et al., 2021). Regarding in vivo research studies, supplementation of various doses of black seed ethanolic extract (350, 250, 150 mg/kg), thymoquinone 20 mg/kg and 100 mg/kg silymarin regularly averted the proliferation of hepatocellular cancer stimulated by diethylnitrosamine by means of numerous pathways, decreased P-ERK 1/2 and P-EGFR, signalled inactivation of EGFR/ERK1/2, decreased hepatic enzymes and α-fetoprotein, downregulated selected genes, subdued cell proliferation and intensified antioxidant enzyme levels (Shahin et al., 2018). Further in vivo research proposed a defensive activity of the thymoquinone and seed oil of *Nigella sativa* against cancer-causing agents in breasts with dose ranges between 1 and 10 mg/kg (Linjawi et al., 2015).

Antihyperlipidemic and Cardio-Protective Effects of Black Seed

The therapeutic effect of *N. sativa* on metabolic syndrome, diabetes mellitus, lipid profile disorder, endothelial dysfunction, atherogenesis, contraction abnormality

in cardiac muscles, platelet aggregation, deranged heart rate, cardiotoxicity and blood pressure disorder has been documented in several in vitro and in vivo experiments. As a result, *Nigella sativa* could be employed as a preventive and therapeutic agent in cardiovascular problems as a safe multipotential plant with high antioxidant and anti-inflammatory effects (Shabana et al., 2013). A few studies have looked into the plant's cardio-protective properties. Numerous studies and contradictory data reported the cardiovascular effects of the plant and its elements. Dehkordi et al. discovered that taking oral *N. sativa* seed extract for two months could lower blood pressure in people with mild hypertension. Both systolic blood pressure (SBP) and diastolic blood pressure (DBP) values were considerably lower after treatment with 2.7 and 5.3 mg/kg/day of the plant extract compared to the baseline. In addition, when compared to baseline data, *N. sativa* supplementation significantly lowered total and LDL-C concentrations. None of the complications was observed during the study in both placebo and experiment groups (Dehkordi & Kamkhah, 2008).

Effects of Nigella sativa *on the Nervous System*

Black seed and its constituents as favourable neurotherapeutic agents for enhancing memory and learning have been studied recently (Beheshti et al., 2016; Sahak et al., 2016). In rodents, 1 ml/kg of black seed oil fortnightly decreased the levels of ROS (reactive oxygen species), enhanced neurogenic proteins and depleted neurocognitive indicators in chlorpyrifos (a pesticide) exposure (Imam et al., 2018). It should be stated that thymoquinone is the most beneficial and identified constituent of *Nigella sativa* and can be considered a beneficial agent for the management of nervous system ailments. The outcomes of many research studies have demonstrated that this herb can improve anxiety, neurotoxicity, memory impairment, pain, epilepsy, depression and neurodegeneration (Beheshti et al., 2016).

Gastroprotective Effects

One of the studies evaluated the effects of black seed in contrast with the triple regime (the standard course of management against *Helicobacter pylori*), including omeprazole, clarithromycin and amoxicillin in patients with dyspepsia (without an ulcer). All of the patients were distributed arbitrarily into four categories. One group received triple therapy only; the second group received 13.3 mg/kg of black seed per day and 40 mg of omeprazole; around 27 mg/kg per day of black seed and 40 mg of omeprazole were prescribed to the third group; whereas the fourth group was reported to receive 40 mg of omeprazole and *Nigella sativa* (40 mg/kg per day). All subjects were advised to take the prescribed medicines for up to one month. The clinical trial outcomes revealed that *Nigella sativa* at a dose of around 27 mg/kg and omeprazole has a strong effect against the activity of *Helicobacter pylori*. The antimicrobial activity of black seed essential oil content consisting of terpenes, thymoquinone and dihydro-thymoquinone could be accountable for this plant activity. The researchers stated that the adverse effects in the patients taking antibiotics and *Nigella sativa* were analogous to merely a slight gastrointestinal irritation for a short period (Yar et al., 2010).

Anti-Allergic and Respiratory System Protecting Effects of Nigella sativa

The possible application of black seed and its oil in allergic rhinitis cases has been verified in clinical and research studies. Nikakhlagh et al. (2011) demonstrated in a prospective and randomised controlled trial (double-blind) that the oral consumption of 6 mg/kg of black seed oil regularly for up to one month in the complaint of allergic rhinitis considerably reduced the intensity of pulmonary symptoms such as nasal itching, mucosal congestion of nose, sneezing, runny nose, mucosal pallor and hypertrophy of nasal turbinates (Nikakhlagh et al., 2011). Furthermore, another study (Rezaeian & Amoushahi Khouzani, 2018) explored black seed nasal spray outcomes in a RCT. In this trial, subjects in the test group received around 1 gram (two puffs) of black seed nasal spray per day, while the placebo group received the NaCl spray (0.65%) at two puffs per day. Another study also mentioned that according to the Lund-McKay-Kennedy test scoring system, 22 scores were utilised, and the results were considerably lesser in the test group than in the placebo. These outcomes are consistent with the former reports related to the antihistamine properties of black seed (Boskabady & Sheiravi, 2002; Kanter et al., 2006).

Antiobesity Effects of Black Seed

Numerous preparations of the black seed, including powder, oil and extract, demonstrate a substantial role in altering blood lipids and work as a remedy for different diseases such as obesity, diabetes, cardiac disorders, metabolic syndrome and fatty liver. Thymoquinone has also been documented for its dyslipidemia-managing capability. Various clinical trials of NS supplementation in patients with dyslipidemia also demonstrated it to have a beneficial effect in treating hyperlipidemia and hypercholesterolemia, especially in patients with diabetes (Razavi & Hosseinzadeh, 2014). A research trial of *Nigella sativa* powder was carried out on almost 39 male adult patients having central obesity for approximately 90 days with a 1.5 gm dose regularly. Remarkable positive outcomes were noticed in waist and hip ratio, systolic BP, waist circumference and body weight, while there is a decrease in FBS, serum testosterone, uric acid, diastolic BP and triglyceride. Moreover, aspartate aminotransferase and serum glutamic pyruvic transaminase levels also reduced substantially (Mathur et al., 2011; Najmi et al., 2008; Vanamala et al., 2012).

Antihypertensive Effects

Thymol, one of the active constituents of *Nigella sativa*, has been demonstrated to decrease blood pressure by obstructing the calcium channels, and the mechanism can be described by including the reduction of calcium ion secretions from the membrane-bound structure of muscles, i.e. sarcoplasmic reticulum and decline in sensitivity of calcium ions or obstruction of calcium influx throughout the membrane in cells (Peixoto-Neves et al., 2009). Oil of *Nigella sativa* has been revealed to reduce in vivo angiotensin-converting enzyme, apparently utilising its capability to decrease angiotensin II production. Interestingly, the activity of cardiac heme oxygenase-1 demonstrated a considerable rise in rodents managed with the oil of *Nigella sativa* at

the dose of 2.5 mg per kilogram for around two months. It is acknowledged that heme oxygenase-1 plays a significant role in decreasing blood pressure by decreasing NADPH oxidase and angiotensin II-arbitrated oxidative stress (Jaarin et al., 2015).

Numerous research studies are documenting positive outcomes of black seed use in high blood pressure. A study reported that consumption of black seed extract (100–200 mg for up to two months) in mild high blood pressure cases brought about a considerable drop in both systolic and diastolic blood pressure contrasted with placebo. Simultaneously a substantial reduction in LDL and total cholesterol was seen, and no issues were developed due to this treatment. Similar outcomes were attained by the black seed oil (Dehkordi & Kamkhah, 2008). Another research revealed that its consumption in a 2.5 ml dose twice a day for up to two months decreased both diastolic and systolic BP in volunteers with good health (Salehi et al., 2021).

Toxicological Effects of *Nigella sativa*

In rodents, *Nigella sativa* oil's toxicological effects were evaluated by assessing its possible haematological, biochemical and histopathological outcomes and estimates of LD50 values. The LD50 values of *Nigella sativa* acquired by only one dose, intraperitoneally and orally introduced in rodents, were around 29 ml/kg of body weight per oral and around 2.1 ml/kg of body weight correspondingly. Additionally, chronic toxicity was evaluated in mice regularly managed with an oral dose of 2 ml/kilogram of body weight for around three months. Alterations in the levels of crucial liver enzymes such as GGT, AST and ALT, and moreover, histopathological changes in body organs such as liver, pancreas, heart and kidneys were not identified in mice managed with black seed after approximately three months of management. The serum glucose, triglyceride and cholesterol levels and the platelets and leucocytes count reduced considerably, contrasted with control values, while haemoglobin and haematocrit levels enhanced substantially. Moreover, there was no proof of toxicity in the liver after consuming the seeds of *Nigella sativa* (Tennekoon et al., 1991).

Conclusion

Nigella sativa can be considered one of the 'bounties from nature' because of its essential nutritional constituents and numerous health benefits. *Nigella sativa* seeds are rich in a range of phytochemicals, among which the health benefits of some of the constituents are yet to be studied and verified. However, most of them are proven to be beneficial pharmacologically and tend to protect the body against many life-threatening diseases such as hypertension, cancer, stroke, paralysis and cardiovascular diseases. Several medicinal uses of black seed have been confirmed by in vitro and in vivo studies. However, further research studies and clinical trials are still required, particularly those associated with chemical changes in the active constituents of *Nigella sativa*, which may discover any new lead molecule or health benefit.

Moreover, a wide range of research projects on particular molecular and cellular mechanisms of action, in addition to randomised controlled trials for establishing its effects in humans, is the need of the hour to analyse the use of *Nigella sativa* in infections, especially in drug-resistant microbial strains, hypertension, cardiac arrhythmias, post-stroke complications and other diseases.

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Chapter 15

Nutritional and Medicinal Properties of Camel Milk

Introduction

Camels, the members of the family *Camelidae*, are of two types, i.e. (i) *Camelus dromedarius* (one-humped or Arabian camel) and (ii) *Camelus bactrianus* (two-humped or Bactrian camel (El-Agamy et al., 1992). Camels play a considerable role in the manner of living for several societies, specifically those living in the Arabian regions and dry Middle East zones (Kaskous, 2016). The global population of camels is around 29 million, relying on the most current FAO (Food and Agriculture Organization) statistics, among which approximately 95% are *Camelus dromedarius* (single-humped) camels (Sikkema et al., 2019).

Camels are brought up for meat, milk, fibre/wool, transport and other purposes, and their dung (gobar) is utilised as fuel (Park & Haenlein, 2006). The meat of camels is a great animal protein source in several Asian and African regions, particularly in areas where the weather negatively influences the production effectiveness of other species of animals. The culinary practices, moreover the palate for meat, in numerous Arabian and African countries have changed to prefer the flesh of camels instead of meat from other species of animals due to their beliefs in its therapeutic benefits, accessibility and/or cost-effective price (Kadim et al., 2013). Camel meat is healthful since the animal has low cholesterol levels compared to other animals' meat and is also comparatively high in PUFAs (polyunsaturated fatty acids) in contrast with beef (Abrhaley & Leta, 2018; Dawood & Alkanhal, 1995). This is a remarkable factor in decreasing the risk of cardiovascular disorder, which is associated with the consumption of saturated fat. Camel meat is also consumed to mitigate ailments such as hypertension, pulmonary disorders, hyperacidity and pneumonia, moreover as an agent to enhance sexual desire (aphrodisiac) (Kurtu, 2004).

Meanwhile, the milk of camels is identified for its healing properties, which are extensively used to preserve human health in different countries, i.e. the developing countries and the ex-Soviet Union (Konuspayeva et al., 2009). The lactation period in camels may range from nine to 18 months, while the quantity of milk acquired relies upon several factors such as stage of lactation, breed of camel, the health status of

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the animal and biological conditions (Swelum et al., 2020). The yield of camel milk is decreasing and unstable as compared to the yield of cow milk (Park & Haenlein, 2013).

Thousands of people around the globe are taking milk regularly because of its wonderful nutritional values such as being an excellent source of vitamin D and calcium; moreover, it helps in the growth and development of children though it also has established benefits for people of old age, particularly in menopausal women where lack of calcium is a high-risk factor for causing osteoporosis (El-Hatmi et al., 2006). Camel milk is a wholesome diet consisting of all the nutritional constituents. Camel milk consists of vitamins, minerals and fats in higher amounts and has extremely high energy. Camel milk demonstrates immunostimulatory effects and is effortlessly digested in the stomach; moreover, it is well accepted by children who are deficient in lactase enzyme and are allergic to cow milk (Ahamad et al., 2017; Al-Awadi & Srikumar, 2001; El-Agamy et al., 2009; Yateem et al., 2008).

Recently, camel milk was also stated to have other healing properties, such as managing hepatitis C infection (Redwan & Tabll, 2007), reducing blood pressure (Salami et al., 2009), anti-diabetic properties (Korish, 2014), management of autism (Shabo & Yagil, 2005), wound management in patients of diabetes (Badr, Badr, et al., 2012; Badr, Ebaid, et al., 2012) and hypoallergenic effects (Katz et al., 2008).

Furthermore, camel milk has been stated to have therapeutic values against several diseases such as food allergies, tuberculosis, dropsy, anaemia, jaundice, piles, spleen disorders and asthma (Hamad et al., 2011; Singh et al., 2017). It is revealed that camel milk has a useful impact on patients with chronic fatigue, chronic liver disease and can be used as an adjunct to mother's milk (Sharmanov et al., 1978) since camel milk is distinguished by a comparatively potent defensive system contrasted with other species' milk (Singh et al., 2017).

Camel milk products include cheese, soap, ice cream, pasteurised milk, milk powder and latte coffee that have been manufactured and sold in numerous countries (Al Haj & Al Kanhal, 2010). Khalesi et al. (2017) documented that people living in dry rural areas of Africa and Asia consume camel milk as biomedicine to manage numerous health problems, such as oedema, asthma and diabetes, as camel milk consists of high levels of vitamin B3 and vitamin C and is also loaded with Fe and Cu as compared to bovine milk (Park & Haenlein, 2006).

The prime focus of this chapter is to review the unique nutritional composition and therapeutic properties of camel milk (especially that of *Camelus dromedarius*); moreover, its beneficial effects in humans such as anticancer, hepatoprotective, antioxidant, hypoallergenic and anti-diabetic properties. Camel milk demonstrates considerable biological activities, and it's quite protective and efficacious against heavy metal toxicity (Al-Hashem et al., 2009) and moreover bacterial and viral infections (El-Agamy et al., 1992). The southeast Asian population consumes camel milk for the management of different kinds of conditions such as jaundice, anaemia and diabetes. The statistics were again validated by the patients with diabetes getting camel milk—one of the principal manufacturers of camel milk is Saudi Arabia (Ahamad et al., 2017). In children, camel milk has been documented to manage acute food allergies that were unresponsive to modern treatments (Shabo et al., 2005).

Composition of Camel Milk

Milk is considered a wholesome food for recently born mammals throughout the early developmental stages (Shah, 2000). The composition of camel milk has been researched in several regions of the world (Al Haj & Al Kanhal, 2010).

The density of camel milk varies from 1.026 to 1.035 while the pH varies from 6.2 to 6.5; both are lesser in contrast with cow milk, and the highest skimmed milk's buffering capability is at 4.95 pH (Gul et al., 2015). Camels' health status, genetic makeup, feeding situations, physiological and seasonal variations were stated to affect the camel milk composition. However, seasonal variations and geographical outset were established to be the most effective factors in the composition of camel milk. In 2009, Konuspayeva et al. reported the impact of geographical origin on the composition of camel milk and demonstrated that the composition of milk obtained from East African camels has a greater content of fat in contrast with milk from camels residing in western Asia and Africa (Konuspayeva et al., 2009). Generally, the average quantity of constituents in camel milk is 87% water, 4.4% lactose, 3.5% fat, 3.4% protein and 0.79% ash (Al Haj & Al Kanhal, 2010) (Figure 15.1).

Numerous vitamins such as vitamins A, B1, C and E and minerals such as Mg, Na, Cu, Ca, K, Fe, P and Zn are found in camel milk (Abrhaley & Leta, 2018; Onjoro et al., 2003). The trace minerals' values were considerably greater in camel milk than in cow milk. The vitamin C concentration in camel milk is two- to three-fold greater than cow milk, and decreased pH because of greater vitamin C concentration stabilises the milk, and hence it can be stored for comparatively longer durations without developing a layer of cream. The accessibility of a comparatively greater amount of vitamin C in camel milk is of remarkable relevance from the dietetics perspective since it provides strong antioxidant activity (Abrhaley & Leta, 2018).

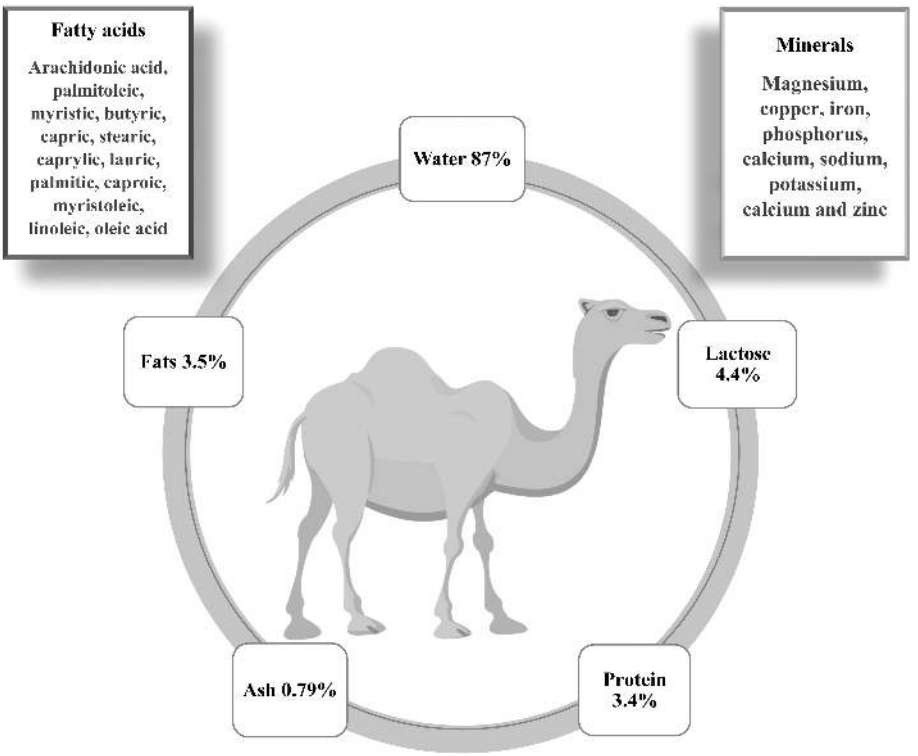

Figure 15.1 Nutritional values of camel milk.

Several FAs such as arachidonic, palmitoleic, myristic, butyric, capric, stearic, caprylic, lauric, palmitic, caproic, myristoleic, linoleic and oleic acid are present in camel milk (Narmuratova et al., 2006).

It lacks β-lactoglobulin and has a minimum quantity of β-casein, which are usually present in cow milk and may cause allergy (Shabo et al., 2005). Defensive proteins in camel milk include peptidoglycan identification protein, lactoperoxidase, immunoglobulins, lactoferrin, N-acetyl-g-glucosaminidases and lysozymes which have healing properties, while little nanobodies of camel milk protect from allergies caused by food and enhance immunity (Shabo et al., 2005). The lactoperoxidase enzyme of camel milk works against gram-negative and gram-positive strains of bacteria (Yaseen & Hanee M, 2019). Camel milk also consists of zinc in greater amounts that are essential for the development and preservation of the immune system and for enhancing immunity (Habib et al., 2013). Researchers thought that the antibodies of camel milk could be beneficial against HIV, hepatitis C, cancer and Alzheimer's disease (Habib et al., 2013; Shabo et al., 2005).

Fermented Camel Milk Products

The milk products, either camel or bovine with health-enhancing benefits, are fermented by lactic acid bacteria (Ayyash et al., 2018). The in vitro health-enhancing benefits of camel milk fermented products have also been documented (El-Salam & El-Shibiny, 2013). Several products manufactured from camel milk (dromedary) include butter (Al Haj & Al Kanhal, 2010), yoghurt (Hashim et al., 2009), soft cheese (Al Haj & Al Kanhal, 2010), ice cream and fermented milk. The yoghurt prepared from camel milk (without preservatives) was documented to have a quite soft texture and was thin with a good flow. The mixing of both calcium chloride (0.075%) and sodium alginate (0.75%) with camel milk was stated to create bearable firmness and form identical to that of yoghurt synthesised by the milk of bovine animals (Al Haj & Al Kanhal, 2010; Hashim et al., 2009).

Hypoallergenic Effect of Camel Milk

For newborn infants, the milk of mothers gives the optimum nutrition throughout the initial stages of life, though a number of infants are merely partially breastfed or not breastfed at all. Therefore, several alternatives to human milk can be used, for instance, soymilk and formula of considerably hydrolysed milk protein (El-Agamy, 2007). Scientists state that 10 to 20% of children having an allergy to bovine milk can't tolerate derivatives of soy either (Businco et al., 1992; El-Agamy et al., 2009; Maldonado et al., 1998; Zeiger et al., 1999). Milk of *Camelus dromedarius* was recently prescribed as an alternative to bovine milk for children who have allergies to the milk of bovine animals. Mother's milk was stated to be hypoallergenic because it is rich in β-casein protein and has a low quantity of α_s-CN (El-Agamy et al., 2009); it also has a lack of β-lactoglobulin (Kappeler, 1998) and resemblance of the antibodies (Shabo et al., 2005). In infants, the milk of bovine animals demonstrates a high rate of allergenicity since it has a high rate of β-lactoglobulin (El-Agamy, 2007) and α_s-CN (Taylor, 1986) in milk proteins. In 2009, El-Agamy et al. initiated an in vitro research dependent upon sera of humans synthesised from blood samples of

40 children suffering from allergy to bovine milk or milk products. The researchers documented that camel milk could be a novel source of protein for children who have an allergy to milk from a bovine source. Camel milk is anticipated to cause slight hypersensitivity reactions since the percentages of milk protein in camel milk are identical to that established in the milk of humans (El-Agamy et al., 2009).

Antioxidant Activity

Salami et al. researched the antioxidant activity and enzymatic digestibility of α-lactalbumin from camel milk that demonstrated greater extents of hydrolysis with chymotrypsin and trypsin enzymes compared to bovine α-lactalbumin; however, both of them revealed analogous susceptivity for enzyme pepsin. Camel's α-lactalbumin's antioxidant capability was higher than that of α-lactalbumin of bovine animals since it consists of greater amino acid remnants, and furthermore, variations in conformational attributes of both proteins. The impact of enzymatic hydrolysis with camels' whole casein digestive enzymes and b-CN on their antioxidant activities was researched. Subsequent to enzymatic hydrolysis, the free radical scavenging effects of camels' β-casein and whole casein were increased (Kumar et al., 2016; Salami et al., 2009).

β-casein of camels demonstrated great free radical scavenging effects and subsequent hydrolysis with chymotrypsin. One of the research outcomes proposed that when camel milk is taken and digested, the synthesised peptides begin to work as natural antioxidants. Currently, one of the studies compares the antioxidant property of peptide fragments from camel and bovine milk fermented by *L. rhamnosus* PTCC 1637. The outcomes revealed that greater antioxidant activity was noticed in cultured camel milk in contrast with bovine milk (Moslehishad et al., 2013; Singh et al., 2017).

Anti-Infective Properties of Camel Milk

McCann et al. (2006) separated two antibacterial peptides from bovine animals, i.e. AS1 and AS2 casein; these peptides demonstrated antibacterial activity in opposition to the gram-positive microbe. Strains of *Lactobacilli* have been stated to give rise to antibacterial substances such as bacteriocins, lactic acid and diacetyl which are contemplated to have inhibitory effects on other microbes and infectious agents (Alhaj et al., 2018). Camel milk was established to show antibacterial effects against gram-negative and gram-positive microbes (Benkerroum et al., 2004). This might be because of the existence of natural antibacterial substances in camel milk, including immunoglobulins, lactoferrin, lysozyme and lactoperoxidase (El-Agamy et al., 1992). At the same time, the inclusion of *L. rhamnosus* in camel milk was researched recently, which was demonstrated to show angiotensin-converting enzyme I activity (Moslehishad et al., 2013). The inclusion of *Lactobacillus helveticus* 130 B4 in the milk of the Mongolian camel resulted in the synthesis, segregation and recognition of angiotensin-converting enzyme I peptides (Quan et al., 2008). Numerous peptides of ACE I acknowledged in the literature were developed from proteins of bovine milk introducing only strains of *Lactobacillus helveticus* or in blend with *Streptococcus thermophilus*, and the inclusion of *Streptococcus thermophilus* to milk

was demonstrated to give rise to the synthesis of peptides that were active against infectious agents during fermentation of milk (Alhaj et al., 2018). Camel milk is loaded with lactoferrin with strong anti-inflammatory and antibacterial properties, including microbial reduction (*H. pylori*, *E. coli*, *Clostridium*, *Staphylococcus aureus* and *Klebsiella pneumonia*), antimycotic effects (*Candida albicans*), immunomodulating effects, antiviral (cytomegalovirus, HIV, HSV-1, hepatitis virus), anticancer and antioxidant activities (Abdel Gader & Alhaider, 2016). Antibodies of camel milk act against *Mycobacterium tuberculosis* and also prevent viral infections (Yaseen & Hanee, 2019). Scientists have concluded that camel milk has favourable effects in patients with multiple-drug-resistant tuberculosis (Mohammadabadi, 2020).

Camel milk has antibacterial activity against several infectious agents including *Escherichia coli* and *Listeria monocytogenes* (Ayyash et al., 2018). Lactoferrin in camel milk is extremely potent and reduces *Schistosoma mansoni* (Redwan & Tabll, 2007). Camel milk decreases the growth of *Candida albicans*, *Klebsiella pneumonia*, *H. pylori*, *Escherichia coli*, *Staphylococcus aureus* and species of *Clostridium*. It also acts against HSV-1, hepatitis B, HIV, cytomegalovirus and hepatitis C virus (Rasheed, 2017).

Anti-Diabetic Activity of Camel Milk

Diabetes mellitus and its complexities have become a centre of attention for researchers all around the globe because of their close relationship with the risk of cardiovascular and cerebrovascular disorders, which were observed in 68% of diabetes-associated deaths among patients of 65 years of age or above. Nowadays, the treatment of diabetes mellitus continues to be a big challenge for healing physicians. There is rising evidence that consumption of camel milk is beneficial in controlling diabetes mellitus in both experimental animals and humans. Additional validation comes from the most current finding that the intake of camel milk by patients with type I diabetes ensued in a 30 to 35% decrease in the regular insulin requirements, with considerable reductions in both micro-albuminuria and levels of blood glucose (Abdel Gader & Alhaider, 2016).

These advantages can be associated partly with the unique camel milk composition loaded with immunoglobulins, minerals (Alhaider et al., 2013), insulin-like proteins and insulin (Malik et al., 2012); and moreover, a few elements in trace quantities with anti-inflammatory properties. Camel milk also has free radical scavenging and antioxidant abilities (Al-Hashem, 2009; Habib et al., 2013; Korish et al., 2015). Additionally, insulin derived from camels holds distinctive attributes that make it unique from other animals' and human insulin and is found efficacious when given orally. Camel insulin has also been suggested to be enclosed in NPs (nanoparticles), making the absorption uncomplicated and facilitating its passage to the blood flow (Malik et al., 2012). It is also reasonable that the antioxidant activity of camel milk averts the demonstration of metabolic syndrome (MS), including hyperlipidaemia, hyperglycemia and insulin resistance. This, consequently, would reduce the pathophysiological pathways underlying the diabetes mellitus complications such as cardiovascular issues, retinopathy and nephropathy that enhance the morbidity and death rate of the disease (Abdel Gader & Alhaider, 2016; Agrawal et al., 2009; Al-Hashem, 2009).

Hepato-Protective Activities of Camel Milk

Camel milk consists of casein which initiates the programmed cell death of the hepatitis C virus (Almahdy et al., 2011). It is stated that the high quantity of lactoferrin in camel milk acts as a principal therapeutic agent against hepatitis C virus infection and brings about a complete reduction of the virus (Redwan & Tabll, 2007). Besides lactoferrin, immunoglobulin G of camel milk can identify the hep-C viral peptides in contrast with immunoglobulin G of humans (El-Fakharany et al., 2012). Furthermore, camel milk can decrease the multiplication of viral DNA, increase the immune reaction of cells and recuperate patients of chronic hep-B (Saltanat et al., 2009). Almost eight weeks of camel milk intake improved the functions of the liver, enhanced the activity of catalase and glutathione enzymes and decreased inflammatory infiltrations and liver fat (Korish & Arafah, 2013). The high content of vitamin C in camel milk improves hepatic function (Mohammadabadi, 2020).

In a more extensive research study, El-Fakharany et al. (2012) reported the antiviral property of camels' lactoferrin, immunoglobulins-G, alpha-lactalbumin and casein in contrast with three intravenous human immunoglobulins-G, in opposition to hep-C virus, by discovering its pathogenicity in Huh-7.5 and peripheral blood mononuclear cell lines. The outcomes demonstrated that camel lactoferrin and immunoglobulin G prevented the entry of hepatitis C virus into Huh-7.5 and peripheral blood mononuclear cells while alpha-lactalbumin, casein and human immunoglobulins-G failed to prevent or inhibit the entry of hepatitis C virus at any experimented concentration (Alavi et al., 2017).

Anticancer Properties of Camel Milk

Various rationale investigations demonstrated that consumption of camel milk ensues in inhibition of disordered cell development. Therefore, a group of researchers have developed a formulation to control cancerous growth (Sumaira et al., 2020). Camel milk has been revealed to give rise to apoptosis in the human liver and breast carcinoma cells by means of epigenetic processes (Abrhaley & Leta, 2018; Korashy et al., 2012). In 2012, Korashy et al. showed that camel milk persuades apoptosis in MCF7 cells of human breast carcinoma and Hep G2 cells of human hepatoma by means of oxidative and apoptotic stress arbitrated mechanisms. Camel milk aids to reinstate after anti-tumour management by its anti-cytotoxic and antigenotoxic outcomes through reducing MPEs (micronucleated polychromatic erythrocytes) and makes the mitotic indicator of bone marrow cells better (Salwa & Lina, 2010).

Constituents of camel milk decrease the cancer cell growth in colon carcinoma, while the glycoprotein lactoferrin has an increased iron affinity and may assist in the proliferation of cells by carrying iron into the cells.

One of the studies explored the capability of lactoferrin from camel milk to impede the growth of cancer cells. This research has documented that 3–5 mg/ml (high concentrations) of lactoferrin from camel milk diminish the multiplication of HCT-116 cancer cells in the colon by approximately 56%. On the other hand, no considerable reduction of cell multiplication was observed at minimum concentrations, i.e. less than 1 mg. Lactoferrin (Figure 15.2) has also been demonstrated to have a range of biological properties, including antimicrobial activity (Tsuda &

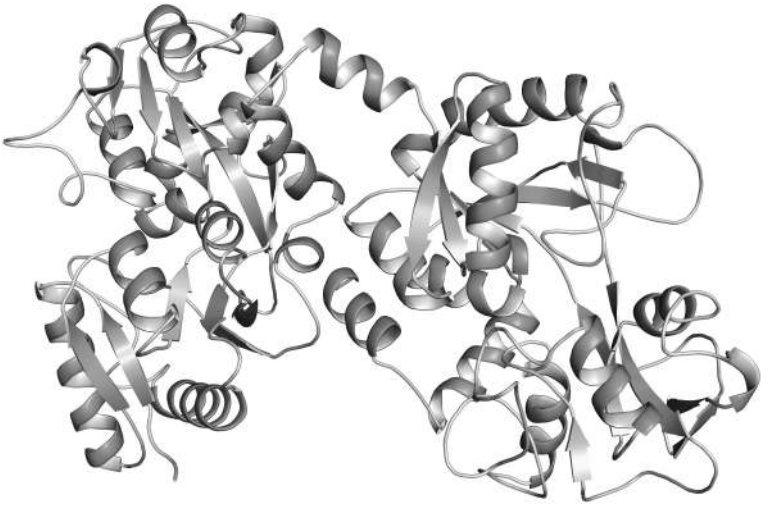

Figure 15.2 Lactoferrin.

Sekine, 2000). Gader and Al-Haider (2016) reported that camel milk could eliminate lung, liver, leukaemia, glioma and colon cancer cells (Abdel Gader & Alhaider, 2016). The dynamic immunoglobulins of camel milk have the capacity to damage tumour cells (Levy et al., 2013). Furthermore, camel milk has blood-clot-dissolving (thrombolytic) activity, which decreases the synthesis of fibrin, thus decreasing the growth of tumour cells (Mohammadabadi, 2020).

Conclusion

Camel milk has captured the attention of several researchers because of its distinct effects on health, and a rising number of research publications have emphasised the therapeutic potential of camel milk along with its particular constituents. The recent publications discussed health-promoting effects and nutritional values of camel milk, such as managing hepatitis C, autism, food allergies and diabetes, removing the toxins from the body and for hepatic disorders. Generally, it appears that camel milk has a strong effect on the management of diabetes and hepatic disorders. Moreover, it can be utilised as an agent to decrease the hazardous effects of toxins. It can be a good substitute for people who have allergies to bovine milk. More research in this domain should be performed to identify the elements included in the effects of health promotion and how these elements work along with camel milk's integration and interactions with other constituents from herbs to prepare a suitable blend for the management of fatal and chronic diseases.

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Chapter 16

Anti-Inflammatory, Antimicrobial and Other Beneficial Effects of *Allium sativum* (Garlic)

Introduction

Allium sativum is the second-most extensively grown *Allium* following onion and has been consumed throughout history for medicinal and cooking purposes. The Indians, Sumerians, earliest Egyptians and Chinese are well recognised to have used garlic more than 4,000 years ago. Among others, Theophrastus and Hippocrates elucidated the use of *Allium sativum* during the Roman and Greek periods (Brewster & Rabinowitch, 2019). Garlic is believed to have initially arrived from southern Europe and Asia, particularly the Mediterranean zone (Thompson & Kelly, 1957), and it was brought to the western regions by the French and Portuguese (Purseglove, 1988). The garlic cloves are the most often consumed plant part, consumed either in uncooked or cooked form; *Allium sativum* typically has a spicy, pungent flavour that pleasantly sweetens and gets significantly smoother with cooking (Peter, 2012).

Although Middle Asia is the indigenous land of garlic (Beshbishy et al., 2019), there are numerous beliefs related to its precise origination, such as that it derives from China, near the mountains of Tien Shan to Kyrgyzstan. Sumerians were diligently using the healing properties of garlic, and there is a belief that they escorted *Allium sativum* to China, from where it was then extended to Korea and Japan. Some analysts still affirm that *Allium sativum* emerged in China (Batiha et al., 2019) in the earliest times of China; garlic was among the most consumed herbal remedies from 2700 BC. Because of its heating and invigorating effects, it was positioned in the yang group. *Allium sativum* was advised for those who endured depression. Consequently, due to these invigorating effects of *Allium sativum*, the people of Japan have not added garlic, in the tradition of Buddha, even though the cuisine of

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Figure 16.1 Fresh garlic.

Japan does not acknowledge garlic either (El-Saber Batiha et al., 2020). In traditional Indian medicine, *Allium sativum* was considered a beneficial remedy utilised as a tonic, roborant and agent to manage cough, haemorrhoids, weakness, lack of appetite, dermatological disorders and rheumatism. The Indian sacred books (Vedas) also talk about garlic, and it was mentioned among other therapeutic plants (Batiha et al., 2019) (Figure 16.1).

Species of *Allium* and their dynamic constituents are stated to decrease the risk of cardiovascular ailments and diabetes, prevent infections by stimulating the immune system and have antifungal, antibacterial and anticancer as well as anti-ageing properties, which was verified by epidemiological research data from clinical trials on humans (Rahman, 2001). *Allium sativum* has been utilised as a spice for culinary purposes that can give a distinct flavour to food throughout the process of cooking. Moreover, it is used for medicinal purposes, including for the management of colds, pulmonary disorders, earache, gastric disorders and whooping cough, and also aids in the prevention of CVD (Badal et al., 2019). Though aged garlic extract (AGE) is a herbal preparation that has been revealed to boost the immune system and hence reduce cardiovascular disorders and cancer, fresh garlic and its modified products have been stated to consist of different constituents of sulfur that have been added into different kinds of preparations (Mathew & Biju, 2008).

Historical Uses of Garlic

Egyptians were well versed in numerous spicy, toxic, aromatic and medicinal plants. Initially, when they were still destitute and inconsequential, they were contented with their own therapeutic plants among their flora near the River Nile, and *Allium sativum* was the most consumed plant. Afterwards, when they started acquiring power and commercial significance, they were extensively exploring for plants having medicinal properties and with robust aromas, spices and physiological activity

from the eastern regions. The consumption of garlic persisted but now as medicine for the poor and as a food. The tombs of Egyptians are the visible antiquated inscriptions for the subsistence of garlic. The garlic clay sculptures dating from 3700 BC have been ascertained by archaeologists, while garlic demonstrations have been established in another vault from 3200 BC. Several medicinal plants have been stated in the Ebers papyrus, and amid others, the much valued and acknowledged garlic is found to be useful in managing 32 diseases. Tutankhamen, the young ancient Egyptian ruler, was sent on his trip to life far beyond the grave accompanied by garlic as a preserver of his wealth and promoter of his soul.

The sacred book of the Jews, the Talmud, advises taking food along with garlic each and every Friday. Moreover, the Bible also mentioned a meal with cheese and garlic, which used to be eaten up by harvesters or farmers. Hippocrates also prescribed garlic as a drug against parasitic infestations and as a diuretic and laxative. Dioscorides advised *Allium* as a remedy for modulating the menstrual cycle, as an anthelmintic, against seasickness and for alleviation of colic.

He also suggested the use of garlic for snakebite and against the bite of the insane dog (for that reason, they directly smeared garlic on the affected area). Consequently, the Greeks named *Allium sativum* a snack grass. *Allium sativum* was carried to the island of the UK (Great Britain) in 1548, from the Mediterranean Sea, where it was found in a very large quantity. In 1564, Lonicerus advised the use of garlic topically for dandruff (seborrhea), for a variety of dermatological disorders and against helminths (parasites).

In earliest Europe, it was consumed without any limitations—especially in Italy, whereas the French consumed it by adding it to numerous dishes. With the passage of time, people have acquired the knowledge of making tinctures and herbal teas from garlic and at the same time gained an understanding of mixing honey and garlic in equal proportions etc. Consequently, they overcame numerous infections of the stomach and acquired the knowledge of how to combat fever, diarrhoea and cold, hence enhancing the lives of lots of patients. In 1720, due to garlic, a thousand Marseille residents were protected from the expansion of the plague's epidemic. Louis Pasteur, in 1958, stated that *Allium sativum* destroyed microbes, and it was even found to be effective against some resistant strains of bacteria. He also observed that garlic destroyed *H. pylori*. Moreover, the antiseptic and anti-infective properties of garlic were established in the subduing of diphtheria, typhoid fever and cholera in Beirut. Garlic is also recognised as Russian penicillin because of its extensive usage by Russian doctors for the management of pulmonary disorders; along with other substances, it was utilised as a remedy for children. It was frequently used in the management of a range of diseases during the First World War by German soldiers (Petrovska & Cekovska, 2010).

Chemical Constituents of Garlic

Garlic cloves are stated to have hundreds of plant chemicals, including sulfur constituents, such as allicin, ajoenes, diallyl disulfide, vinyldithiins, diallyl trisulfide and others that comprised 82% of the total sulfur content of garlic (El-Saber Batiha et al., 2020). Allicin, the most organically dynamic sulfur-holding constituent of garlic, is accountable for its taste and smell (Rahman, 2007; Slusarenko et al., 2008), while alliin is the chief allicin precursor, which contains around 70% of overall

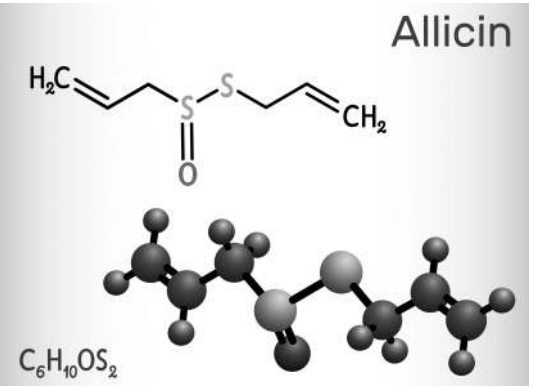

Figure 16.2 Chemical structure of allicin.

thiosulfinates found in the compressed cloves (Kaye et al., 2000). One of the odorant compounds, allyl mercaptan, is accountable for garlic breath and arises from the reciprocal action of diallyl disulfide or allicin with cysteine in the existence of S-allylmercaptocysteine (Kaye et al., 2000; Lawson & Gardner, 2005). However, allicin, PCSO (S-propyl-cysteine-sulfoxide) and MCSO (S-methyl cysteine sulfoxide) are the chief smelly constituents of freshly ground homogenates of garlic (Zeng et al., 2017) (Figure 16.2).

Organosulfur Compounds

Organosulfur constituents are natural constituents consisting of sulfur. These compounds are distinctive due to their unpleasant or disgusting odours, with some exceptions. Organosulfur constituents are naturally found in some animals and plants. They are essential for life because they aid in the management and prevention of numerous hazardous and deadly disorders such as diabetes, neurodegenerative diseases, cancer, CVD, mycotic, viral and microbial infections. Among all the amino acids, cysteine and methionine are organosulfur compounds (Block, 1978).

These compounds can be classified on the basis of sulfur-containing functional groups; a few of them are methionine, dibenzothiophene, lipoic acid, allicin, diphenyl disulfide, sulfanilamide, cysteine and penicillin. *Allium* is among those vegetables that are really known for their distinct flavours and smell, for which a range of organosulfur constituents are accountable (Brewster, 2008). Allicin is beneficial against a broader spectrum of microbes compared to conventional antibiotics (Borlinghaus et al., 2014). Allicin does not present in garlic until it is cut or crushed (Blackwood & Fulder, 1986). Mashing or cutting the garlic bulb invigorates the enzyme alliinase (Walag et al., 2020), which converts alliin to allicin (Block, 1985). Organosulfur compounds drawn out and separated from garlic are often researched with reference to their in vivo antioxidant properties (Yin & Cheng, 2003).

Allicin is the frequently studied organosulfur constituent, and it was initially documented to demonstrate biological activity by Chester John Cavallito and John Hays Bailey in 1944 (Cavallito & Bailey, 1944). Thus, decades of considerable research based on inspecting their biological activities have given proof that allicin has a wide variety of biological effects such as anticancer, antibacterial,

antihyperlipidemic, antidiabetic and anti-angiogenesis effects (Chan et al., 2013; Chu et al., 2013; Fujisawa et al., 2009). S-allyl cysteine extracted from garlic was established to substantially decrease the blood glucose levels in rodents. The blood glucose reducing effect of S-allyl cysteine was ascribed to its sulfur constituent by invigorating the secretion of insulin indirectly or directly. Considerable literature has mentioned cancer-inhibiting properties of organosulfur constituents, including apoptosis, interrupting the cell cycle and differentiation of the cell. Moreover, the compounds are popular in possessing both cancer prevention and cancer managing properties; other organosulfur constituents of garlic, such as allyl sulfides, are identified to have anticancerous activity (Walag et al., 2020).

The organosulfur compounds have cancer-preventing activities, which are achieved by their counteracting properties against carcinogens (Ariga & Seki, 2006). The organosulfur compounds originating from garlic, such as allyl sulfides, are identified to have anticarcinogenic activities (Guyonnet et al., 2004; Milner, 2009). OSC constituents of garlic are identified to comprise both preventive and management properties against cancer (Schäfer & Kaschula, 2014). The strength of sulfides in *Allium* should be protected by keeping away from needless deterioration by means of incorrect processing and cooking to abstain from losing its anticancer properties (Ariga & Seki, 2006).

Pharmacological Uses of Garlic

Antidiabetic Activity

Allium sativum has been demonstrated to inhibit oxidative stress, pathological alterations in streptomycin-prompted type 1 diabetic rodents and pancreatic cell damage (Kaur et al., 2016). Additionally, garlic protects diabetic rodents from diabetic retinopathy. The blood glucose, weight and structural modifications of retinal tissues in the group managed with *Allium sativum* got better after stomach gavage of garlic extract in rats for seven weeks (Albarakti, 2016). Furthermore, AGE had dose-reliant antidiabetic outcomes on streptomycin-prompted diabetic rodents (Thomson et al., 2016); moreover, a meta-analysis was carried out on around 768 persons with type 2 DM in nine RCTs, and the outcome demonstrated that supplements of garlic considerably inhibited HbA1c and fructosamine. This research showed that garlic supplements were efficient in treating type 2 DM (Wang et al., 2017). Consequently, *Allium sativum* and its bioactive constituents might be useful agents in the management of diabetes and its complications (Shang et al., 2019).

Antiviral Activity

Garlic extract has been tested against type 2 rhinovirus, type 3 parainfluenza virus, cytomegalovirus, influenza virus, vesicular stomatitis virus, HSV1, HSV2 and vaccinia virus (Gruhlke et al., 2016). Surprisingly, in vivo research trial showed the antiviral effects of garlic and its extract. They demonstrated that *Allium sativum* has defensive activity against the human influenza virus by enhancing the synthesis of harmonising antibodies when provided to rodents. This activity was established on the existence of numerous chemical constituents of the plant, specifically allicin, methyl allyl thiosulfinate, ajoene and allyl methyl thiosulfinate (Sawai et al., 2008).

Allicin works by protecting lots of thiol enzymes, whereas the antiviral property of ajoene was because of the aversion of adhesive association and combination of white blood cells (El-Saber Batiha et al., 2020).

Antihyperlipidemic Activity

Research studies reveal that garlic can decrease blood cholesterol in both humans and animals. Research demonstrated that raised pressure and temperature processing could pull out the garlic's pungency, and this garlic efficiently decreased the levels of triglyceride, total cholesterol and LDL cholesterol in high fat-fed rats (Sohn et al., 2012). One more study discovered that mixing 1.5% garlic extract in a high-cholesterol diet for male rats could considerably regulate the cholesterol and lipid metabolism and reduce the levels of triglyceride, total cholesterol and blood lipids, which could be caused by the decrease in mRNA expression of the SREBF-1c gene (Ha et al., 2015). In one of the longitudinal studies, the consumption of 300 mg of garlic per day for approximately two months was revealed to decrease the LDL and cholesterol levels. On the contrary, it increases the HDL (high-density lipoprotein) levels; however, *Allium sativum* had no impact on triglyceride levels in diabetic cases with dyslipidemia (Siddiqui et al., 2016). In addition, an aged garlic supplement for around 13 weeks was established to decrease the lipid hydroperoxide and myeloperoxidase activities in blood and to reduce the F2-isoprostanes concentration in urine and plasma of nearly 41 hypercholesterolemic patients. Furthermore, the aged garlic extract had more improved effects as compared to raw garlic (Ho et al., 2016).

Antiobesity Activity

Allium sativum has antiobesity effects and has been demonstrated to prevent the impact of high-cholesterol diet on adipose tissue and body weight in hypercholesterolemic rodents (Yang et al., 2018). Moreover, the oral administration of fermented garlic extract by lactic acid bacteria (LAFGE) decreased the mass of high-fat-diet-fed male rodents (C57BL/6J). Fermented garlic extract by lactic acid bacteria also decreased their mesenteric, retroperitoneal and epididymal fatty tissue mass. The potential MOA was that LAFGE decreased lipogenesis by downregulating the messenger ribonucleic acid and protein expression of C/EBP, PPAR and lipogenic proteins (Lee et al., 2016). Furthermore, the alcoholic extract of black *Allium sativum* was determined to decrease the mass of rodents fed with a high-cholesterol diet. This management modulated lipid metabolism by up-regulating the adenosine monophosphate-activated protein kinase expression, perilipin, forkhead box protein O1 and adiponectin in the fatty tissues of the rodents and downregulating the bunch of differentiation 36 (CD-36), tumour necrosis factor-α, resistin and plasminogen activator inhibitor-1 (K. Chen et al., 2019).

Anti-Inflammatory Effects of Garlic

The organosulfur compounds in garlic were established to have anti-inflammatory effects. Allicin, one of the chief constituents of garlic, was discovered to reduce the

synthesis of cytokine messengers identified to be a proinflammatory medium in research about IBD (inflammatory bowel disease) (Lang, 2004). In another experiment, a constituent obtained from allicin was established to have a potential initiating point as anti-inflammatory medicine with minimum adverse effects (Krishna & Yadav, 2012). Moreover, the ajoene and sulfonyl derivatives were also separated from garlic and identified to have anti-inflammatory properties (Lee et al., 2012). These constituents work as anti-inflammatory agents by decreasing the creation of prostaglandin E2 and nitric oxide and are thought to be a favourable medicinal agent for managing inflammation-related diseases.

Moreover, ajoene was also identified to counteract the activity of COX2 and the secretion of prostaglandin E2. One of the organosulfur constituents of garlic, diallyl trisulfide, has prospective anti-inflammatory activity, and it works by decreasing the cytokines and arbitrates in in vivo and in vitro experiments (Walag et al., 2020). Furthermore, this constituent also demonstrated the capacity of inhibiting LPS (lipopolysaccharide)-prompted foot oedema in rat models. Sulforaphane was also established to be beneficial as a healing agent for managing inflammation-associated disorders (Chen et al., 2009).

Role of Garlic in Cancer

According to some extensive epidemiological studies conducted in Italy, the USA and China, a high intake of garlic considerably decreased the risk of colorectal and gastric carcinoma, occasionally by 50% (Borek, 2001; Fleischauer & Arab, 2001; Greenwald et al., 2001; Steinmetz & Potter, 1996). A tendency towards a relationship between intake of garlic and decreased risk of breast and prostate carcinoma has also been documented (Fleischauer & Arab, 2001). Pre-clinical research experiments constantly demonstrate the preventive effects of aged garlic extract, garlic and its chemical constituents against cancer, decreasing the growth of colon, gastric, mammary and other carcinomas and causing apoptosis of cancer cells (Borek, 2001; Lee, 2008; Milner, 2006). Experiments also demonstrated the capability of AGE in the prevention of healthy cells against cellular death initiated by chemicals and radiation during the treatment of cancer (Borek, 2001, 2004; Li et al., 2009).

Most of the molecular research experiments executed with AGE endorse existing information that organosulfur constituents of garlic decrease the risk of cancer. Moreover, S-allyl mercaptocysteine has been revealed to decrease the multiplication of cancer cells and alter redox signalling pathways, inducing apoptosis and mitotic apprehension (Pinto et al., 2006). AGE was established to reduce angiogenesis, the act required for the growth of tumours (Matsuura et al., 2006), and to enhance immunity (Kyo et al., 2001).

The antioxidant activity of the water-soluble garlic constituents and a few of its fat-soluble constituents play a considerable role in preventing cancer. S-allyl mercaptocysteine and S-allyl cysteine, which are distinctive to the aged garlic extract, have robust radical scavenging activity and the capability to escalate glutathione in cells and decrease peroxidation of lipids, which is related to the development of carcinoma; several fat-soluble organosulfur constituents in AGE and garlic have also been established to exert a preventive effect against carcinoma, partly because of their reactive oxygen species scavenging ability, and also to reduce lipid peroxidation (Borek, 2010).

The preventive outcomes of fresh garlic in considerably reducing the risk of GI carcinoma are well reported (Fleischauer & Arab, 2001; Steinmetz & Potter, 1996); the role of AGE as a cancer-protective agent in humans has now been documented, consequently accompanying the pre-clinical experiments that have enduring efficacy in prevention of cancer (Milner, 2006).

Antimicrobial Effects of Garlic

Allium sativum has been consumed for hundreds of years in different societies to fight infections. It has shown to be successful against the abundance of acid-fast *Bacillus*, gram-negative and gram-positive microbes in recent times. These include *E. coli*, *Salmonella* (Adler & Beuchat, 2002; Johnson & Vaughn, 1969), *Staphylococcus aureus*, *Proteus*, *Pseudomonas* (Cavallito & Bailey, 1944), *Bacillus subtilis*, *Micrococcus* (Sharma et al., 1977), *Mycobacterium* (Delaha & Garagusi, 1985), *Klebsiella* (Bayan et al., 2014), *Helicobacter* (O'Gara et al., 2000) and *Clostridium* (De Wit et al., 1979). It has been reported that the herb endeavours a differential reduction between possibly injurious intestinal bacteria and beneficial gut microbiota (Rees et al., 1993).

The antimicrobial activity of *Allium sativum* is extensively ascribed to allicin. It is identified that allicin has a sulfhydryl-altering property (Wills, 1956) and has the capacity to reduce sulfhydryl enzymes. Glutathione and cysteine impede allicin's thiolation activity. Allicin garlic extract has been revealed to endeavour bacteriostatic activities against several vancomycin-resistant intestinal cocci. A decreasing synergism was noted when consumed in conjunction with vancomycin (Jonkers et al., 1999). The antimicrobial effect of various garlic extract concentrations against the bacteria of dental plaque has been demonstrated in in vitro research (Houshmand et al., 2013); the synergism between garlic extract with ciprofloxacin has been revealed, but not amid garlic extracts and ampicillin (Zain Al-Abdeen et al., 2013). The ginger rhizomes and bulbs of garlic extracted with alcohol (95%) are prescribed to have antimicrobial activity against multi-drug-resistant infectious agents and can be consumed for the prevention of multiple-drug-resistant infections. The most perceptive organism in the mixture was *Pseudomonas aeruginosa* (Karuppiah & Rajaram, 2012). *Allium sativum* is also prescribed as a treatment for MDR-TB (Dini et al., 2011).

The antibacterial potential of garlic is amazing: 100 mg of allicin can be obtained from 50 grams of garlic (Slusarenko et al., 2008). Allicin has been stated to affect over 300 microbes (Fujisawa et al., 2009), including a range of microbes, such as *Helicobacter pylori*, *Mycobacterium TB*, MRSA, *Escherichia coli*, *Staphylococcus* spp, *Klebsiella proteus*, *Streptococcus* spp and *Bacillus* spp (Ankri & Mirelman, 1999). Correspondingly, the allicin cytotoxicity in the vaporous state has also been analysed in pulmonary disease-causing microbes including drug-resistant bacterial strains (Reiter et al., 2017).

During medieval times French priests utilised garlic to protect themselves against the plague, now recognised as a microbial infection. The physicians of Russia and Europe impeded and inhibited infection by directly smearing the poultices of garlic on amputations and wounds during the World Wars. Garlic has also been advised as a mosquito and insect repellant; the plant is a rich source of various metabolites, such as peptides, amino acids, fructooligosaccharides and a range of secondary metabolites, and they play a considerable role in the maintenance of human health (Block, 2005).

Antifungal Activities of Garlic

Extract of *Allium sativum* has also demonstrated encouraging antifungal activities against different infection-causing yeasts. The antimycotic activity of garlic was similar to fluconazole (a reference antifungal drug) (Ankri & Mirelman, 1999; Khodavandi et al., 2011). Correspondingly, *Allium sativum* extracts have been documented to decrease pathogenic mycotic growth, such as *Rhizopus* species, *Penicillium expansum*, *Botrytis cinerea*, *Fusarium* and *Neofabraea alba* (Daniel et al 2015; Danladi & Haruna, 1970) the broad range of antimycotic activities of allicin has also been established against numerous pathogenic plant fungi. Allicin demonstrated favourable antimycotic activities both in vivo and in vitro against some pathogenic plant fungi, e.g. *Plectospherella cucumerina*, *Botrytis cinerea*, *Alternaria brassicicola* and *Magnaporthe grisea* (Curtis et al., 2004; Hahn, 2014; Perelló et al., 2013; Sarfraz et al., 2020).

Adverse Effects and Toxicity

The United States FDA considers garlic non-toxic for humans; however, it can cause gastric distress, especially if consumed in excessive doses by sensitive individuals. To evaluate the safety of *Allium sativum*, various RCTs were carried out; adverse events such as vomiting, dizziness, nausea, headache, insomnia, diarrhoea, flatulence, tachycardia, bloating, heartburn, orthostatic hypotension, obnoxious body odour, flushing and sweating were noticed (Rana et al., 2011). Excessive consumption of uncooked garlic in a fasting state can cause modifications in the flora of the intestine, gastrointestinal upset and flatulence. Furthermore, burns and blister dermatitis were reported from topical applications of raw garlic (Piasek et al., 2009). *Allium sativum* doesn't appear to modify the drug's metabolism. However, contemporary studies on healthy volunteers demonstrate uncertain outcomes concerning the effect of garlic in the pharmacokinetics of protease inhibitors, together with anticoagulants because of its antithrombotic activities (Rahman & Lowe, 2006).

Numerous surgeons suggested ceasing the excessive consumption of garlic up to seven to ten days before any surgery because of its ability to enhance the bleeding time, which was noticed in a patient with spontaneous epidural hematoma (Rahman & Lowe, 2006). Preceding in vivo trials demonstrated that supplementing raw garlic for an extended duration in high doses gave rise to a reduction in weight and anaemia because of RBCs breakdown, while consumption of 5 ml/kg juice of garlic resulted in a gastric injury that ultimately led to fatality (Mathew & Biju, 2008). In addition, the persistent consumption of 50 mg powder of garlic per day may bring about anti-androgenic outcomes by decreasing spermatogenesis in rodents, leading to reduce the concentration of sialic acid in the epididymis, testes and seminal vesicles with decreased function of Leydig cells (Rana et al., 2011). Oxidative hemolysis is the principal mechanism of toxicology from *Allium*-acquired sulfur constituents, and it is differentiated by the production of Heinz body and development of methemoglobinemia in the red blood cells (Salgado et al., 2011). At first, numerous clinical indications were noticed, including diarrhoea, vomiting, anaemia, weakness, abdominal pain, rapid respiratory rate, depression, jaundice, hemoglobinuria, loss of appetite and rapid heart rate (Salgado et al., 2011). The toxic symptoms of *Allium sativum* may emerge after a day or several days of its consumption

depending upon the amounts consumed (Lee et al., 2006); prior studies have stated the cardiovascular outcomes of *Allium sativum*, including possibly irreversible fibrinolytic, anticoagulant and antiplatelet activity. There is a substantial reduction in the accumulation of platelets and varied activity on fibrinolytic potentiation (Borrelli et al., 2007). Another research showed that desiccated powder of raw garlic, when given orally, ensued in acute injury to the stomach's mucosa (Chen et al., 2019). Thus experimental studies recorded that garlic in low doses is safe to consume; however, medicinal doses might originate mild disturbances in the GI tract, and extreme doses have been stated to be the reason for hepatic damage (Almogren et al., 2013; Rana et al., 2011; Ried & Fakler, 2014). A membrane-penetrable constituent, allicin can easily enter the cells and work together with thiols such as cysteine or glutathione protein residues (Borlinghaus et al., 2014; Lu et al., 2011; Miron et al., 2000), as well as enzymes consisting of responsive cysteine, and this is probably the prospective elucidation of allicin's toxicity (Gruhlke et al., 2016). Fascinatingly, Rana et al. (2011) showed that garlic powder or allicin at 200 mg per ml concentration can give rise to considerable damage to cells in the separated liver of rodents.

Conclusion

Garlic is one of the most commonly used culinary and medicinal herbs, consumed for thousands of years. It holds a range of phytochemical constituents such as organosulfur compounds, phenolic compounds, saponins etc. It demonstrates several pharmacological uses such as anticancer, antimicrobial, antihypercholesterolemia, antidiabetic, antifungal, anti-inflammatory, antihypertensive, hepatoprotective, immunomodulatory and nephroprotective effects. Further investigations are required to identify its potential, the mechanism of action of each constituent and the ways to process garlic while simultaneously preserving its constituents. Moreover, special emphasis should be given to its toxicity and interaction with certain foods and conventional medicines.

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Chapter 17

Camellia sinensis

Immunological and Other Health Benefits of Tea

Introduction

Tea, as an evergreen plant, has been regularly consumed for thousands of years. After water, tea is the second most-consumed drink on this planet. The tea plant or *Camellia sinensis* belongs to the *Theaceae* family, which is indigenous to China. Later, it was brought to Japan by Buddhist priests, and then it further spread to India, Russia and European countries, etc. Eisai, a Zen priest who was famous for introducing the tradition of tea in Japan, published a book on tea and its health benefits in 1211, named *Kitcha-Yojoki*, in which he also explained the procedure of how to reap and collect the tea leaves, the method of producing tea and the pharmacological outcomes of tea. There is an ancient Chinese proverb that 'Better to be devoid of foodstuff for three days, than tea for 1', and as stated by Lu Yu, the writer of *The Classic of Tea*, 'Tea balances the mind, modulates the soul, dispels lethargy, alleviates fatigue, prevents sleepiness and stimulates the thought' (Lu & Carpenter, 1997). Black tea, oolong and green tea all derive from the same plant, i.e. *Camellia sinensis*; however, their flavours, organoleptic evaluation and chemical composition vary due to their process of oxidation and fermentation. The gratifying astringent flavour and reinvigorating boost tea offers are so deep-penetrating that its prospective health values and therapeutic properties are often ignored or unnoticed. Constant scientific investigation suggests that the precise potential health values originating from tea have significant consequences on human health (Sharangi, 2009). A theory of TCM says that green tea has refreshing and calming features as its taste is bittersweet.

Moreover, it is stated in the Chinese book of *Food and Nutrition* that green tea can enhance alertness, clear the mind, decrease stress and make the mood better

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(Vinson, 2000). However, in Japan during the Tokugawa period, medical physician Ekiken Kaibara specified in his book *Yojokun*, which is about health promotion, that consuming green tea for a longer period is not useful because it eliminates body fat and ultimately causes weight loss (Kaibara, 2008). In eastern parts of Asia, it has been considered widely for ages that tea has therapeutic efficiency in preventing and managing numerous ailments, so life expectancy is frequently related to the consumption of tea. Concerning Chinese history, around 4,700 years ago, Emperor Sheng-Nong established that a regular cup of tea could disintegrate numerous toxins in the body. In acknowledgement of their likely significance in vascular health, polyphenolic compounds, for instance, catechins of tea, were formerly known as vitamin P (Rusznyák & Szent-Györgyi, 1936). Archaeological confirmation essentially antedates this legend and proposes that tea was initially drunk in the early Stone Age period (almost 5,000 years ago). Tea was initially consumed as a medicine and was contemplated so efficaciously that by the fourth century, it was a significant part of life for Chinese people and was consumed to manage a range of diseases, including fatigue, poor vision, rheumatic aches, pulmonary and renal issues (Cooper, 2012).

Classification of Tea

In general, tea can be categorised according to its manufacturing processes as oolong tea (partially fermented), green tea (non-fermented) and black tea (completely fermented). Green tea is principally drunk in China and Japan, while black tea is mostly used in India, Pakistan, Bangladesh, western regions and other global areas. The worldwide manufacturing of green tea reported only 20% of the overall quantity of tea manufactured, which is around one-fourth of that of black tea (Thakur et al., 2012). The leaves of green tea are manufactured by steaming unprocessed or raw tea leaves at raised temperatures to deactivate the enzymes responsible for polyphenolic oxidisation. Green tea is prepared by brewing and consists of numerous polyphenols that are capable of dissolving in water, for instance, catechins. The most important catechins are epicatechin, epicatechin gallate, epigallocatechin and epigallocatechin gallate; 200 millilitres of green tea provides 17, 28, 65 and 140 milligrams of these catechins, correspondingly (Smith, 2011). Several other constituents are also found in green tea, including theanine, theobromine, caffeine, GABA, vitamins, theophylline and 3,4,5-trihydroxy benzoic acid (Chow & Hakim, 2011; Shukla, 2007). Meanwhile, black tea is manufactured by stimulating the enzymatic oxidation of raw tea leaves. The overall level of the catechins is decreased by this method from 40% in green tea to 10% in black tea. Theaflavins, catechins and thearubigins may account for 2–6%, 3–10%, and more than 20% of the desiccated weight in infused black tea, correspondingly (Yang & Hong, 2013). The caffeine content in black tea is identical to that in green tea. Oolong tea comprises theaflavins, catechins and thearubigins; moreover, infused tea may have catechin levels of 8 to 20% of the overall dry material (Shukla, 2007). Numerous derivatives of polyphenols, for instance, chaflosides and theasinensins, are also found in it (Ishida et al., 2009; Yang & Hong, 2013). One of the Japanese green tea brands with great catechins content comprises 154 milligrams of catechins and 23 milligrams of caffeine/100 millilitres. A research study in Japan disclosed that lots of people consume more than ten cups/day (Imai et al., 1997). In this regard, their intake of catechins is approximated to be more than 800 milligrams per day.

Chemical Constituents of Camellia sinensis

The chemical constituents of tea leaves comprise vitamins, volatile oils, amino acids, alkaloids, catechins, flavonoids, polysaccharides, theanine, lipids, inorganic components (for instance, fluorine and aluminium), etc. (Sharangi, 2009). Numerous constituents of tea have particular health benefits; for instance, catechins (polyphenolic compounds) are related to the anti-atherosclerotic, anticancer, antiobesity, antimicrobial, antidiabetic, antiviral and anti–dental caries consequences of tea (Hayat et al., 2015; Kaibara, 2008; Suzuki et al., 2016; Yang et al., 2014). Ascorbic acid makes the immune system stronger and prevents cataracts and scurvy (Sorice et al., 2014; Suzuki et al., 2016). α-ABA and theanine reduce BP and control the functions of the nervous system (Isemura et al., 2015; Suzuki et al., 2016) (Figure 17.1).

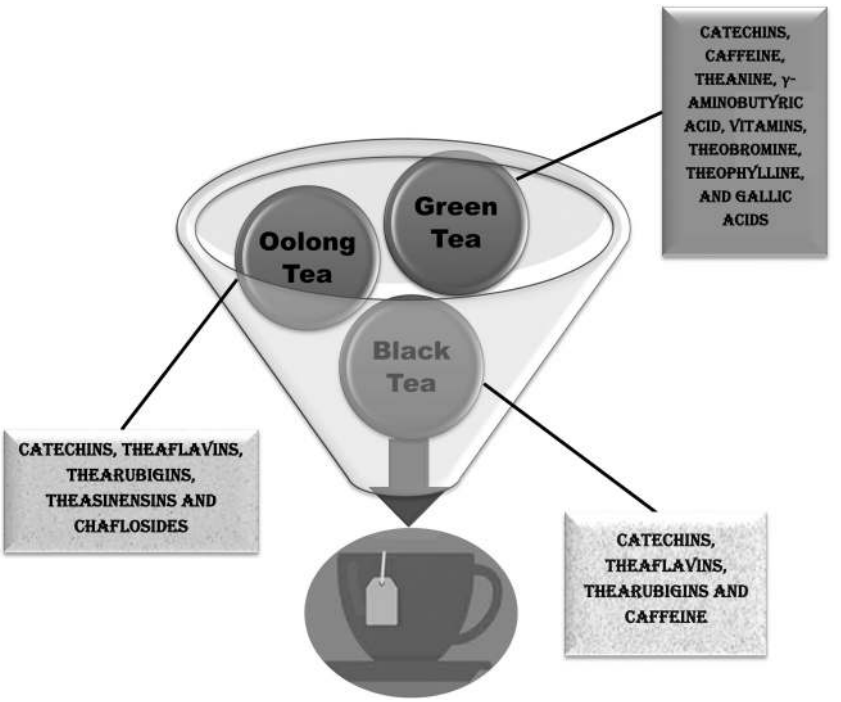

Figure 17.1 *Camellia sinensis*: classification of tea and its chemical constituents.

Pre-Clinical and Clinical Studies on Therapeutic Uses of Tea

A research study that was executed between 2003 to 2006, with 6,472 contributors, establishes that obesity was conversely related to intake of hot tea as the people who have consumed hot green tea had decreased body mass index and mean waist circumference in contrast with those who didn't consume tea. On the contrary, consumption of chilled tea was established to be linked with greater waist circumference, body mass index and more thickness of hypodermic skin folds after adaptation

of mystifying factors, for instance, intake of sugar (Vernarelli & Lambert, 2013). In Poland, an observational, population-based study of 8,821 participants was conducted and established that those tea consumers who take three or more cups of tea per day had decreased body mass index and waist circumference; however, they had raised diastolic BP in contrast with consumers of little tea. The quantification to analyse the strength of association (i.e. odd ratio) between metabolic syndrome and intake of tea was 0.79; obesity and FBS are negatively linked with consumption of tea among the components of metabolic syndrome in women but not in men (Grosso et al., 2015). EGCG has the maximum biological activity among all the catechins present in green tea. In the Netherlands, an initial research study also revealed that excessive dietary consumption of flavonols, flavones and catechins was conversely related to BMI in women (Hughes et al., 2008). Studies on the health-related advantages of consuming tea, principally green tea, are discovering stimulating consequences, predominantly in research related to oncology. Contemporary studies in both western and Asian countries have provided promising results demonstrating that consuming green tea contributes to combating numerous types of carcinomas including oesophagal, ovarian, gastric and colon, as studied by Cooper et al. (2005a, 2005b). Though consuming *Camellia sinensis* is related to alleviation of stress, scientific confirmation of the relaxing and calming properties of tea is sparse. Research studies have revealed that the intake of black tea boosts an optimistic mood and sustains attentiveness. Tea is frequently drunk under situations that encourage relaxation, and these states may contribute to the evident and noticeable relaxation uses of tea (Cooper, 2012). Numerous in vitro experiments demonstrated that tea polysaccharides showed antitumour prospects. Tea seed polysaccharides considerably reduced the growth and multiplication of commemorated cell K562 of myelogenous leukaemia with ($p < 0.01$) and a reduction ratio of $38.44\% \pm 2.22\%$ (Wei et al., 2011). Tea polysaccharides extracted from selenium-enriched green tea of 'Ziyang' considerably decreased the multiplication of human osteosarcoma cancer cells in a dose-reliant way. Tea flower polysaccharides demonstrated powerful inhibitory action on human gastric carcinoma cell growth. An in vivo experiment revealed that tea polysaccharides also aid in diabetes mellitus as they had an inhibitory effect on raised blood glucose levels. Moreover, there have been several research projects showing that tea polysaccharides have numerous other benefits for health including anti-ageing, antioxidant, antioncogenic, antimicrobial as well as the capability to enhance immunity, restrain or prevent diabetes and decrease hepatotoxicity (Du et al., 2016).

Health Benefits of Tea

Type 2 Diabetes Mellitus and Tea

Numerous research studies have described the antidiabetic consequences of green tea. A huge cohort study was executed and established that drinking coffee, green tea and overall caffeine was related to a decreased risk of type 2 diabetes mellitus, though none of the associations was established between intake of oolong or black teas and the likelihood of type 2 diabetes (Iso et al., 2006). Another longitudinal study conducted in 26 centres in eight European regions, with an aggregate of 340,000 contributors and follow-up of 4,000,000 person-years, demonstrated that

tea consumption was inversely related to the occurrence of type 2 diabetes mellitus (The InterAct Consortium, 2012). The outcomes of case-control research carried out in China with nearly 4,800 participants showed that the intake of oolong tea or green tea might protect against the development of type 2 diabetes mellitus, principally in those who consume 16 to 30 cups in a week (Huang et al., 2013). It has been proven by several studies that green tea aids in regulating the levels of blood sugar; it also helps in burning body fat, assisting in weight loss in all those patients who are suffering from metabolic syndrome (a forerunner of T2D). Research studies propose that Japanese people who drink six or more cups of green tea per day have a 33% decreased risk of developing T2D, contrasted with those who drink one cup of green tea per day or less. The decline of risk emerges to be more affirmed in women contrasted with men (Iso et al., 2006).

Tea and Stress

In recent times, researchers have associated L-theanine with the emotional state of relaxation reported by those who consume green tea. Investigational research projects have also revealed that L-theanine seems to refute particular effects of caffeine. L-theanine eases the origination of α-waves in the brain assumed to be related to an alert yet relaxed mental state. A scientific study on L-theanine employing young females as research participants revealed that L-theanine appeared to have the highest impact on the generation of α-waves among those females who had been classified as subjects of raised anxiety (Talbott, 2007). Theanine is considered to decrease levels of cortisol in the period of stress. This organic relaxant functions to reduce worry, stress and apprehension, permitting the nervous system to concentrate and focus better (Cooper, 2012).

Role of Tea in Obesity

An epidemiological survey disclosed that intake of warm or hot tea was conversely related to obesity. The consumers of tea had considerably decreased mean circumference of waist and reduced body mass index compared to non-consumers of tea (Vernarelli & Lambert, 2013). One research study revealed (Nagao et al., 2007) that the constant intake of green tea that is loaded with catechins led to a drop in body fat, low-density lipoprotein cholesterol and systolic BP. The consumption of Pu-erh tea had noteworthy effects on 36 preobese Japanese adults by decreasing the body mass index, mean circumference of the waist and values of the fat that is stored within the abdominal cavity (Kubota et al., 2011). Outcomes from numerous research studies propose that the reduction of pancreatic enzyme lipoprotein lipase may be included in the antiobesity activities of tea constituents (Yuda et al., 2012). Epigallocatechin gallate reduced pancreatic lipase in a non-competitive way concerning the concentration of substrate; epicatechin gallate demonstrated similar restraining activity (Grove et al., 2012).

Prevention of Cancer

Up till now, considerable attention has been given to the cancer-preventing and cancer-managing functions of tea and its catechins with cell and animal trials. From

the enormous volume of printed papers on models of animals, the general conclusion is that a great number of studies have recorded the cancer-protective activity of catechins (present in tea) against oncogenesis at various sites of the organ with profound evidence (Kanwar et al., 2012; Yang et al., 2009). Tea and its chief constituents, for instance, epigallocatechin gallate and tea polyphenols, introduced in the body through diet or water, have been proven to decrease carcinogenesis in numerous animal models for distinct organ sites, comprising the oesophagus, buccal cavity, lung, stomach, small or large intestine, liver, skin, pancreas, urinary bladder, mammary glands and prostate. Even though it was considered that epigallocatechin gallate and other catechins are the most important active constituents of tea in the reduction of oncogenesis, an epidemiological study proposes that caffeine also demonstrates efficient restraining activity in the skin and lungs (Yang et al., 2011). Additionally, the tea polysaccharides found in the flower of tea are stated to have considerable anticancer activities (Xu et al., 2012). The utilisation of research studies to validate the association between the risk of cancer and intake of tea has been confirmed to be challenging. In 1989, Oguni and his coworkers detected that the frequency of deaths from gastric carcinoma in males of Nakakawane, Japan, was around one-fifth of the average for all Japanese men and advised that this low rate may have been related to the ingestion of green tea (Oguni et al., 1989). One of the contemporary studies showed an inverse relationship between the consumption of green tea and distal stomach carcinoma among Japanese women (Sasazuki et al., 2012). Several studies on humans also described an inverse association between the risk of carcinoma and ingestion of black tea. For example, McCann et al. noticed a noteworthy inverse relationship between the risk of endometrial carcinoma and intake of more than two cups of black tea per day (McCann et al., 2009).

The Immunological Aspect of EGCG from Green Tea

The association between the immune system and green tea has been recognised for hundreds of years in eastern nations, while western nations have only been well informed of its advantages for a small number of decades (Vinson, 2000). In contrast with some other foods, green tea demonstrates numerous prospective benefits for the health of humans, without the undesirable adverse effects of synthetic medicines, which makes it an optimistic part of the research. A remarkable association currently detected is that Asian peoples who regularly drink green tea enjoy an extensive life expectancy and decreased frequency of ailment compared to western peoples (Hicks et al., 1996). From the immunological point of view, laboratory research projects had proposed that epigallocatechin gallate is a powerful, strong and extensively efficient anti-inflammatory constituent that can reduce the production and multiplication of numerous molecules of the immune system that can be responsible for injuries or damage to joints and other inflammation (Singh et al., 2011). Following one of the research's results, epigallocatechin gallate reduces imiquimod-persuaded psoriasis-identical inflammation of BALB/c (albino, laboratory-bred strain of the house rodent) (Zhang et al., 2016). Psoriasis chiefly disturbs the T lymphocytes, and the interleukin-23/interleukin-17 strain is principally considered to be serious in its pathogenesis. In one of the studies conducted on mice that have a psoriasis strain, the imiquimod cream was locally applied to mice for six successive days to manage the symptoms of the disease. Throughout the experiment, local application and management with epigallocatechin gallate were

controlled distinctly, and the outcomes of the two methods were noticed in mice with psoriasis-identical inflammation and irritation of the skin. The outcome indicates that local application of epigallocatechin gallate decreased the intensity of psoriasis-like inflammation and irritation of the skin, making the pathological structure of the skin better by decreasing the manifestation of epidermal PCNA (Pal et al., 2015). Current research studies propose that epigallocatechin gallate can alter the power of both the adaptive and innate disease-preventive capabilities of the immune system (Min et al., 2015). The studies conducted by Min et al. were to investigate the immuno-modulatory outcomes and MOA of epigallocatechin gallate on inflammation of joints or arthritis in investigational mice (Min et al., 2015). *Camellia sinensis* encourages the benefits of health by influencing the immune system. EGCG is without a doubt the principal catechin in green tea, which comprises around 50 to 80% of the overall 200 to 300 milligram prepared teacup of green tea. Epigallocatechin gallate is a biochemically dynamic constituent with identified antioncogenic, anti-inflammatory, and free radical–hunting properties. Additionally, there are several research projects executed that confirm the preventive ability of epigallocatechin gallate against carcinoma (Singh et al., 2011).

Anti-Ageing Effects of Tea

It is revealed by one of the in vitro studies on biologically aged HDF that tea polysaccharides stimulated the multiplication of human diploid fibroblast considerably, whereas the anti-ageing outcomes of tea polysaccharides on human diploid fibroblast were even more powerful than tea polyphenols and vitamin C (Du et al., 2016). The capabilities of tea polyphenols and tea polysaccharides to shelter the skin were evaluated utilising four aspects, that is, absorption, moisture, sunscreen and retaining power, encouraging the multiplication of fibroblast cells and inhibitory capacity of tyrosinase. Refined tea polysaccharides had better moisture-absorbing and retaining abilities than tea polyphenols. Tea polyphenols sheltered skin against the ultraviolet radiation of the sun, increased rapid multiplication of fibroblasts (connective tissue cells that secrete collagen) and had a depressing effect on the enzyme tyrosinase, while purified tea polysaccharides barely guarded the skin against ultraviolet radiation and displayed a weak capacity to repress enzyme tyrosinase. Tea polyphenols and tea polysaccharides had harmonising benefits, and they should be suitably united to attain greater functioning when applied as dynamic constituents in cosmetics (Wei et al., 2009). A half-yearly RCT (double-blind) study on healthy postmenopausal women demonstrated that a nutritional supplement comprising the extract of white tea and protein polysaccharides of fish provided better structure, form and firmness of the skin in postmenopausal females, revealing improvement around the eyes, around the oral orifices, above the eyebrows or in the frontal region, under-eye dark circles, sagging skin, blotched pigmentation, laxity and general appearance (Skovgaard et al., 2006) (Figure 17.2).

Adverse Effects of Green Tea

All the aforementioned teas are comprised of theanine and caffeine, which distress the brain and appear to intensify mental vigilance (Huynh, 2016). The data from the study conducted by Takabayashi revealed that a high dose of epigallocatechin

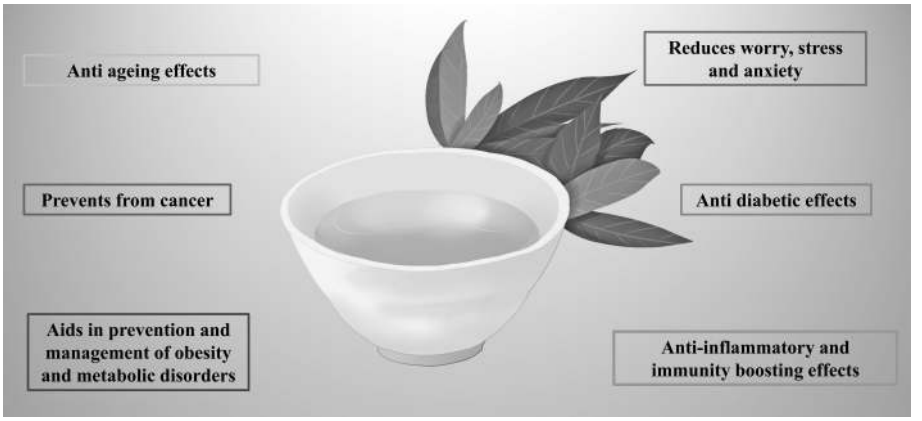

Figure 17.2 Benefits of consuming tea.

gallate in green tea had an influence on oxidative deoxyribonucleic acid impairment in the liver and pancreas of rodents (Takabayashi et al., 2004). This carries apprehensions about consuming the supplements of green tea rather than ingesting the green tea. Throughout the day, numerous people drink other caffeinated drinks, for instance, colas and coffee, so the overall caffeine they take will be greater and could be the reason for unfavourable and unpleasant effects, for instance, headache, nervousness, abdominal ache, tremors, vomiting, nausea and diarrhoea (Lin et al., 2014). Another research revealed that extract of green tea repressed in vitro production of human immunoglobulin E in a dose-dependent manner utilising a mechanism except for cytotoxicity (Hassanain et al., 2010). Though the destruction of immunoglobulin E could be worthy in definite cases, there are two foremost apprehensions. Primarily, we are not acquainted with the accurate dosage that will function in humans. The measured quantity of 300 nanograms per millilitre concentration of green tea extract was utilised to demonstrate the effect in vivo and in vitro. A human requires advanced doses because humans are far larger, and sufficient doses need to be consumed. Yang et al. state that ingesting 3.0 grams solid green tea along with 500 millilitres of water would acquire 326 nanograms per millilitre of epigallocatechin gallate in the plasma. Though, if more than 3 grams are ingested, the concentration of epigallocatechin gallate in plasma remains 326 ng/millilitre. Yang proposed the reason that it was because of the occurrence of saturation. Therefore one must know about the accurate dosage and methods to intake tea so that it can bring benefits to health. Another apprehension regarding green tea is that it comprises polyphenol which has little bioaccessibility in serum. When people consume green tea, its bioactive constituents could have a distinct influence contrasted with the consequences from research laboratory trials due to the binding of protein and metabolism. Moreover, the mechanism of suppressing immunoglobulin E synthesis by green tea extract is unidentified (Yang et al., 1998). Mazzanti and colleagues (Mazzanti et al., 2009) stated that the consumption of a green tea supplement was related to hepatic damage. Thus, the consumption of supplements with high content of catechin and green tea that comprises exceptionally high concentrations of catechins must be avoided or be taken with great caution. Another study (Tsubono et al., 2001) specified that the consumption of green tea in men might be related to a

greater risk of gastric carcinoma. The consumption of black, green and oolong teas may similarly intensify the danger of cancer in the urinary bladder (Lu et al., 1999). Green tea was held accountable for causing asthma in nearly 21 cases reported by Shirai et al. (1997). Additionally, hypersensitivity pneumonitis was observed in a 51-year-old male who received inhalation therapy of tea catechin for one month and treatment for TB for 3.5 months (Suzuki et al., 2016).

Conclusion

Verification or confirmation of facts associated with the health benefits of tea plants or *Camellia sinensis* concerning numerous research projects is present. However, contradictory outcomes have also been recorded, which shows that further studies are required to better understand the benefit/risk ratio in diverse varieties of tea. Additional research is also required to make known the fundamental biological mechanisms of the activities of various kinds of tea. However, the consequences of human studies, which have established the inverse relationship between the death rate and intake of tea, propose that people may be capable of enjoying endurance of health by consuming tea.

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Chapter 18

Lemongrass

Medicinal Benefits and Uses

Introduction

Lemongrass belongs to the family *Poaceae* and is a perennial grass that is distributed evenly and established in tropical areas (Francisco et al., 2011). Central and South America extensively utilise this plant because of its medicinal values and gratifying taste (Bensabah et al., 2015; Coelho et al., 2016). It is broadly recognised by the name citronella or lemongrass; however, because of its distribution, it is identified by multiple names (Table 18.2). The word *Cymbopogon* is derived from the Greek word '*Kymbe-pogon*', which means boat-beard (because of the configuration of its flower spikes), and the meaning of *citratus* is lemon-fragrant leaves (Shah et al., 2011). Research findings have documented around 55 species of lemongrass, among which approximately three of the species, i.e. Jammu grass (*Cymbopogon pendulus*), Malabar grass (*Cymbopogon flexosus*) and lemongrass (*Cymbopogon citratus*), are distributed extensively (Chowdury et al., 2015; Clement et al., 2015; Kouame et al., 2016; Lawal et al., 2017). Lemongrass has elongated, tiny and needle-like leaves of about 1.3–2.5 centimetres in breadth and around 0.9 centimetres long, with bluish-green glossy colour, loose tips and a fragrance of citrus when pulverised because of the existence of citral and the great amount of aldehyde geranial and neral (Oladeji et al., 2019; Tajidin, 2012). The blade of the leaf is around 18 to 36 centimetres, while the plant doesn't make panicles or flowers (Oladeji et al., 2019) (Table 18.1).

Lemongrass or *Cymbopogon citratus* is frequently consumed in curries, soups and teas. It is also appropriate for seafood, fish and poultry (Shah et al., 2011). Lemongrass is so-called because of its characteristic citrus fragrance in the leaves, especially when they are pulverised. It is also recognised as 'citronella' or 'squinant' in English, with other familiar names all over the world (Haque et al., 2018). The pleasing fragrance of lemon from this grass has extensively been utilised in associated cosmetics, food industries and perfumery (Ranade & Thiagarajan, 2015).

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Table 18.1 Taxonomic Classification of Lemongrass

Kingdom	Plantae
Phylum	Magnoliophyta
Class	Liliopsida
Order	Poales
Family	*Poaceae*
Genus	*Cymbopogon spreng*
Species	*Citratus*

Table 18.2 Vernacular Names of Lemongrass

Name of the country	*Identified name*
United States of America	Citronella
Nigeria	Elephant grass
Egypt	Lemongrass
Chinese	Xiang mao
Malaysia	Sakumau
French	Citronelle
Turkish	Limon out
Italy	Cimbopogone, citronella
Sri Lanka	Sereh
Swedish	Citrongrass

Primarily, lemongrass was utilised to add some flavours to the Vietnamese and Thai cuisines. It has been consumed in regions of South America and Africa for adding flavours to the tea. It is also famous for non-alcoholic and alcoholic drinks (Preedy, 2016). Furthermore, it has been used traditionally in Ayurveda as an anti-inflammatory, diuretic, tranquilliser and antipyretic medicine (Carlini et al., 1986; Haque et al., 2018). There are several examples of the lemongrass application in different health remedies by diverse ethnic groups. Tea prepared from leaves of lemongrass is consumed principally as an anti-inflammatory, sedative, antispasmodic, analgesic, diuretic and antipyretic blend in Brazil (Leite et al., 1986; Souza Formigoni et al., 1986). In Cuba, it is utilised for reducing blood pressure and managing rheumatism and catarrh, as well as to manage the empacho (difficulty in food digestion because of overeating certain foods) and sore throat in Argentina (Carbajal et al., 1989; Filipov, 1994). Moreover, numerous biological activities of *Cymbopogon citratus* have been documented for many years, including but not limited to antirheumatic, antifungal, antioxidant, antimicrobial, anti-inflammatory, cardioprotective, antiseptic, antiprotozoal, antitussive, antirheumatic and anticarcinogenic activities (Ekenyong et al., 2015) (Table 18.2).

The genus of *Cymbopogon* is extensively dispersed in the subtropical and tropical areas of America, Asia and Africa, consisting of around 144 species, and this genus is popular for its great quantity of essential oils which have been utilised for applications in perfumery, cosmetics and pharmaceuticals. *Cymbopogon citratus* and

Figure 18.1 *Cymbopogon citratus* (lemongrass).

Cymbopogon flexosus are cultivated commercially in Comoros Island, Madagascar and DRC (Democratic Republic of the Congo). However, the chief exporter of these herbs is Guatemala, which is trading around 250,000 kilograms annually, while the area of the former USSR sells around 70,000 kilograms annually. The trade values of some species of *Cymbopogon* are further increased by their capacity to grow in extreme and unpleasantly rough conditions of climate (Avoseh et al., 2015).

These plants have established a suitable application as grass brooms and roof thatches in places where they are not utilised for medicines, cosmetics or perfumes, such as in South Africa (Shackleton et al., 2007). In Nigeria, they are utilised to manage stomach upset, as a treatment of malaria, as an antioxidant and as insect repellant (Avoseh et al., 2015). The prevailing species in Western and Eastern India are *C. flexuosus* and lemongrass, which have been locally employed in pesticides, cosmetics and the management of fevers and digestive diseases (Desai & Parikh, 2012; Jeong et al., 2009) (Figure 18.1).

Phytochemical Constituents

The secondary metabolites in every plant are specified by their capability to give protection against abiotic and biotic stress (Ballhorn et al., 2009). The defence mechanism differs from one plant to another, their climatic differences and environmental situations. However, these metabolites are found to be in very small quantities; numerous molecular mechanisms are accessible to either decrease or increase the number of certain metabolites by obstructing the competitive routes and enhancing the optimal metabolites (Verpoorte & Memelink, 2002). The management potential of therapeutic herbs could be related to the existence of secondary metabolites and plant chemicals. These constituents are evenly distributed in therapeutic plants. The significant constituents such as L-linalool, flavonoids, phytosterols, organic acids, fatty acids, isovaleric aldehyde, p-coumaric acids, fumesol,

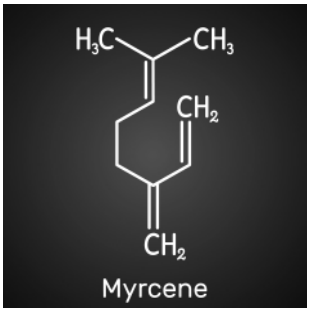

Figure 18.2 Chemical structure of myrcene.

anthocyanin, phenolic constituents, amino acids, valeric esters, isopulegol, volatile compounds, furfurol and methylheptenone have been separated and distinguished from *Cymbopogon citratus* (Moore-Neibel et al., 2012; Paula et al., 2014; Rahim et al., 2013).

Separation of 2-O-rhamnosyl isoorientin, luteolin, isoscoparin and luteolin 7-O-glucoside from the rhizomes and leaves of *Cymbopogon citratus* has been documented. Other constituents of flavonoids separated from the aerial parts of lemongrass are apigenin, kaempferol and quercetin (Cheel et al., 2005), while chlorogenic acid, hydroquinone, elemicin, caffeic acid and catechol from the aerial fragments of similar species are also separated (Avoseh et al., 2015).

Studies have demonstrated that the constituents of terpenoids in the essential oil of *Cymbopogon citratus* vary in accordance with the genetic variations, plant parts used, geographical origin, extraction methods, maturity stage and harvesting season (Idrees et al., 2012; Ewansiha et al., 2013). In spite of the variations mentioned, myrcene (Figure 18.2) continues to exist as a distinct constituent of this species in fluctuating quantities (Bossou et al., 2013; Kuete, 2017). However, *Cymbopogon citratus* has been stated to consist of a high quantity of citral around 80%, which is a blend of geranial and terpenoids neral and is accountable for the lemon-like smell that distinguishes the species (Kuete, 2017).

A number of studies were carried out to discover the particular biological activities of various compounds in the essential oil of *Cymbopogon citratus*. It was stated that geraniol and citral are accountable for fungicidal activity, while the existence of myrcene increases the antifungal activity further. Phenols, linalool, cinnamic aldehydes and alkaloids were accountable for the antibacterial properties of *Cymbopogon citratus* (Haque et al., 2018; Moleyar & Narasimham, 1992; Onawunmi et al., 1984; Pattnaik et al., 1997). It is more likely that the antimicrobial activity of *Cymbopogon citratus* is an outcome of the collective action of its constituents in contrast with only one constituent (Ekpenyong et al., 2015).

Pharmacological Uses of *Cymbopogon citratus*

Numerous bioassays have verified the strength of *Cymbopogon* species for their multiple utilisations. Lemongrass was established to have chemopreventive activity by protecting the diethylnitrosamine-persuaded hepatocellular damage in rodents (Puatanachokchai et al., 2002). In South Africa, lemongrass extract was utilised for the management of oral thrush in cases who were found positive for AIDS and

established to be effective (Wright et al., 2009). Another species of *Cymbopogon*, i.e. *Cymbopogon martini*, has also been researched, and its essential oil is established to demonstrate high anthelmintic effects against *Caenorhabditis elegans*. *Cymbopogon citratus*, *Cymbopogon giganteus* and *Cymbopogon schoenanthus* essential oils from West Africa all demonstrated around a 100% death rate against *Anopheles gambiae* (Avoseh et al., 2015). Reduction of the early stage of hepatocarcinogenesis was also noticed in *Cymbopogon citratus* (Puatanachokchai et al., 2002).

Anti-Inflammatory Activity

Chronic or persistent inflammation is one of the dominant health challenges all around the world and has been associated with life-threatening disorders such as tumour development or carcinoma (Colotta et al., 2009). Organic products have been consumed in traditional medicines to fight the rising inflammation in humans. The ethnopharmacological research about *Cymbopogon citratus* described its use as natural anti-inflammatory medicine in Asian and African countries. The constituent citral, which is taken out from the *Cymbopogon citratus*, has intensely decreased the mediators of inflammation and acts as additives in ointments and creams to manage the local inflammations. It has also been documented to repress the TNF-α stimulated adherence of neutrophils at 0.1% concentration (de Cássia da Silveira e Sá et al., 2013), decrease the synthesis of NO (nitric oxide), iNOS (inducible nitric oxide synthase) and pathways induced by lipopolysaccharide (Francisco et al., 2013) and bind covalently to the receptors, thus inhibiting the pathways of NF-ɛB (nuclear factor kappa B) (Francisco et al., 2013). Lemongrass also causes suppression of PPAR-α and COX-2 by around 60–70% (Katsukawa et al., 2010) and 80–90% reduction of tissue inflammation topically and orally (Boukhatem et al., 2014). Particular segregated constituents and derivatives from *Cymbopogon citratus* such as glycoside (O–,C–), carvone, peritoneal and 6,7-epoxycitronellal, citral, luteolin, 8,9-epoxycarvone, epoxyestragole, 6,7-epoxycitronellal and 6,7-epoxycitral have decreased the secretions of nitric oxide and prostaglandins related with inflammations (Sepúlveda-Arias et al., 2013). The mediators that have anti-inflammatory properties connect the aglycone and sugar moiety and suppress the pain and postoperative cramps recognised with surgery by inhibiting the identified pain mediating expression (Nishijima et al., 2014).

Antinociceptive Effect

The essential oil of lemongrass has a considerable antinociceptive effect. Contrasting the outcomes acquired with three diverse experimental nociception models, it can be speculated that the essential oil of lemongrass works at both central and peripheral levels (Viana et al., 2000).

Insect Repellent and Insecticidal Activity

Negero Gemeda et al. (2014) conducted in vitro research in an Ethiopian public health facility to investigate the insect-killing activity of certain traditionally utilised Ethiopian therapeutic plants against *Melophagus ovinus* on naturally affected sheep.

Cymbopogon citratus was one of the medicinal herbs investigated in this research for its insect-killing potential against *M. ovinus*. Hence, the essential oil of *Cymbopogon citratus* has a significant insecticidal effect, according to the findings. According to the outcomes of research, lemongrass killed around 100% of *M. ovinus* at a concentration of 3.13µl/mL in almost three hours of exposure, and mortality of sheep ked escalated as the exposure and concentration period to the essential oil enhanced (Gemeda et al., 2014). Additionally, the in vivo insect-killing activity of *Cymbopogon citratus* was investigated further against sheep ked at three various concentrations, and the results revealed a favourable effect on different days after treatment (Gemeda et al., 2014). The essential oil of lemongrass was evaluated against sheep ked at various doses, and the results revealed good insecticidal activity against *M. ovinus* at the minimum concentration for several days after management. Following 7, 14, 28 and 49 days after therapy, various concentrations of *Cymbopogon citratus* essential oils have a similar effect on decreasing *M. ovinus* parasites as regular Diazinon. On 7, 21, 35, 42 and after 56 days of treatment, *Cymbopogon citratus* essential oil at a concentration of 0.3125% shows lower adverse effects on *M. ovinus* parasite in sheep than the simple medication used in this study (Gemeda et al., 2017). The repellent activity of lemongrass essential oils was also evaluated in vivo, and the results showed that the essential oil of this plant was extremely efficient to repel the *P. duboscqi* (an adult sand fly). Because of its excellent efficiency at extremely low concentrations, the essential oil was chosen as a prospective natural repellent to be utilised against *P. duboscqi*. Generally, the outcome of this investigation reveals that the essential oils of *Cymbopogon citratus* exhibit substantial repellent properties against *P. duboscqi* (adult sandflies) at physiological concentrations (Kimutai et al., 2017).

Anti-HIV Activity

The human immunodeficiency virus, in general, is identified as one of the most fatal infectious diseases all around the world. Human immunodeficiency virus-acquired immunodeficiency syndrome has been declared to have a high death rate. The Africans have the greatest number of AIDS patients, and only in South Africa, 1,500 people are daily infected with the virus of HIV. There are numerous symptoms and signs associated with AIDS though oral thrush is frequently observed in AIDS patients, which the extract of lemongrass can manage. The water simmered with *Cymbopogon citratus*, when applied to the thrush, was found capable of managing the oral thrush caused by *Candida albicans* within one to five days (Wright et al., 2009).

Antifungal Activity

One of the studies conducted by Shah et al. (2011) mentions that oil of *Cymbopogon citratus* is functional against dermatophytes fungal infections such as *Microsporum gypseum*, *Trichophyton rubrum*, *Trichophyton mentagrophytes* and *Epidermophyton floccosum* and is among the most dynamic herbs against dermatophytes in humans. As stated in one of the studies, the oil of lemongrass is dynamic against fungi found in the storage of food, ringworm and keratinophilic fungi. Moreover, the oil of *Cymbopogon citratus* efficiently works as an insecticide and herbicide due to its natural anti-infectious effects (Ademuyiwa et al., 2015; Shah et al., 2011).

Antidiabetic Activity

Diabetes is a persistent metabolic disorder caused when the pancreatic cells are not capable of synthesising enough insulin or the body is not capable of using insulin efficiently, ultimately resulting in hyperglycemia. Bharti et al. (2013) analysed the molecular docking and in vivo antidiabetic effect of *Cymbopogon citratus* at doses of 800 and 400 milligrams. Their results demonstrate a considerable reduction in insulin, triglycerides and glucose levels which was also verified by docking of the chief constituents. One more study revealed no or least hyperglycemic activity in Wistar rodents managed with lemongrass tea for around 14 days (Leite et al., 1986). Moreover, with the administration of lemongrass decoction orally at 125–500 mg per kilogram, a considerable inhibition in the rate of hyperglycemia was noticed and had been suggested to be due to the enhanced secretion and synthesis of insulin or escalated consumption of glucose peripherally. The differences noticed in research studies had been the outcome of geological differences in the quality and content of the constituents from *Cymbopogon citratus* (Adeneye & Agbaje, 2007). The in vitro antidiabetic activity of lemongrass oil was estimated against type 2 diabetes mellitus by using the α-glucosidase and α-amylase inhibitory effects. A reduction of α-amylase and α-glucosidase was stated correspondingly (Boaduo et al., 2014).

Conclusion

Medicinal plants have unexpectedly and enormously improved primary health care quality in delivering herbal medicines with minimum or no hazardous effects or adverse drug reactions. Lemongrass is one of these herbs, and it is indigenous to tropical regions of South and Central America, Africa, Asia and North America. Lemongrass is utilised as a flavouring agent in the beverage and food industries. Moreover, their applications have been documented in the cosmetics, culinary, detergent and pharmaceutical industries. It has been utilised as anticancer, antiseptic, antioxidant, antimicrobial, anti-inflammatory, analgesic, antifungal and antinociceptive agents in folk medicine. Nowadays, interests in therapeutic plants have been focused on the exploration of the phytochemical and pharmacology screening of secondary metabolites to investigate their medicinal potential and enhance the synthesis of new herbal medicines. The bioactive constituents and essential oils of *Cymbopogon citratus* have been separated, analysed and characterised for their medicinal activities. In trying to improve the pharmacological studies and plant chemicals of lemongrass, considering factors such as the method of procedures, propagation, extraction and time of harvesting should be addressed and monitored. Considering all the mentioned factors will increase the biological activities and physiochemical configuration of the lemongrass and, thus, enhance its commercial value.

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Chapter 19

Moringa oleifera (Drumstick)

A Multipurpose Herb

Introduction

Moringa oleifera, also recognised as 'drumstick', is a species of rapidly expanding tropical plant that belongs to the family *Moringaceae* (Table 19.2), with thick tuberous roots, seeds, plenty of flowers, green leaves and pendulous extended fruits (Milla et al., 2021). The plant is native to northern India, albeit it is established in Madagascar, southwestern regions of Asia and northwestern and southwestern regions of Africa. It has extensively been a part of long-established horticulture, utilised mostly for decorative reasons in areas near the Pacific seaboard of Mexico (Olson & Fahey, 2011), in addition to plantations in Argentina and Bolivia and some other places in the globe (Milla et al., 2021) (Table 19.1).

Moringa oleifera is loaded with nutrients due to a range of crucial plant chemicals found in its pods, seeds and leaves. In point of fact, the drumstick is believed to provide ten-fold more vitamin A in comparison with carrots, 25-fold more iron in comparison with spinach, nine-fold more protein as compared to yoghurt, seven-fold more vitamin C in comparison with oranges, 15-fold more potassium as compared to bananas and 17-fold more calcium as compared to milk (Rockwood et al., 2013). The reality that drumstick is uncomplicated to grow makes it a long-lasting treatment for malnutrition. Regions like Benin and Senegal manage children with drumstick (Kasolo et al., 2010). Children who don't have enough provision of breast milk are inclined to demonstrate malnutrition symptoms. The agents that are prescribed to enhance the synthesis of milk in lactating mothers are termed galactagogues. These agents consist of plant sterols and function as a hormone precursor needed for reproductive development. The moringa plant is loaded in phytosterols such as campesterol, stigmasterol and sitosterol, which are hormones precursors. These

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Table 19.1 Vernacular Names of Moringa

Language	*Name*
English	Drumstick tree
Tamil	Moringa, murungai
Filipino	Mulanggay
Urdu	Sohanjna
Sanskrit	Shobhanjana
Chinese	La ken
Arabian	Rawag

Figure 19.1 *Moringa oleifera.*

constituents enhance oestrogen synthesis, which sequentially invigorates the multiplication of the ducts in mammary glands to synthesise milk. It is consumed to manage malnutrition in younger children (less than three years of age) (Gopalakrishnan et al., 2016) (Figure 19.1).

The genus of *Moringa* consists of several species: *Moringa concanensis*, *Moringa arborea*, *Moringa longituba*, *Moringa stenopetala*, *Moringa pygmaea*, *Moringa oleifera*, *Moringa borziana*, *Moringa ruspoliana*, *Moringa hildebrandtii*, *Moringa rivae*, *Moringa drouhardii*, *Moringa ovalifolia* and *Moringa peregrina* (Abd Rani et al., 2018). Among all of the species, *Moringa oleifera* is one of the most researched and consumed for its pharmacological, nutritional and phytochemical properties. In accordance with Ayurveda, it has featured properties for the management of a number of ailments, such as dermatological disorders, fevers, epilepsy, haemorrhoids, ophthalmic disorders and asthma. As a matter of fact, it is a therapeutic plant traditionally identified in regard to malnutrition and other ailments (Milla et al., 2021).

The extracts of drumstick have been researched for various therapeutic reasons: anti-ulcer, antimicrobial, antineoplastic, anti-inflammatory, hepatoprotective, antioxidant, antihyperlipidemic, antihypertensive, antidiabetic, diuretic and antipyretic (Abdull Razis et al., 2014; Fahey, 2017; Meireles et al., 2020). In 2007, Anwar et al. issued a table with different traditional therapeutic uses of the numerous

Table 19.2 Taxonomic Classification of Moringa

Kingdom	Plantae
Division	Magnoliophyta
Class	Magnoliopsida
Order	Capparales
Family	*Moringaceae*
Genus	*Moringa*
Species	*Oleifera*

parts of *Moringa oleifera* (MO) (Anwar et al., 2007; Meireles et al., 2020). In lots of countries, seeds, leaves, roots and flowers of MO are consumed as medicine for the management of ailments such as cough, hypertension, epilepsy, hysteria, sores, wounds, asthma, dropsy, dermatological infections, headaches, body aches, fever, diabetes, paralysis, diarrhoea, arthritis, general weakness, irritations and tumours. Moreover, they are used as mild diuretics, emmenagogues and expectorants, etc. (Alhakmani et al., 2013; Popoola & Obembe, 2013; Pamok, 2012).

Nutritional Values of Moringa

All parts of the moringa plant have various bioactive chemical constituents, for instance, vitamins, tannins, isothiocyanates, phenolics, glucosinolates, carotenoids, alkaloids, flavonoids and saponins. Pods and leaves of this plant are utilised as vegetables around the Indian subcontinent and in other developing countries. Besides their nutritional values, these parts of the plant are enriched with bioactive constituents, which comprise many pharmacological and nutritional activities. The moringa plant is loaded with vitamin A, vitamin C, potassium, EAA (essential amino acids) and calcium (Shinde & Kamble, 2020). Oleic acid is the most important fatty acid found in the oil drawn out from the seeds of moringa (Anwar et al., 2007). Moringa seeds of various ecotypes differ in the content of n-hexadecanoic acid, (Z)-propionamide, 6-octadecenoic acid, ethyl oleate, 6-octadecenoic acid, oleic acid and 13-docosenamide (Shinde & Kamble, 2020). A greater amount of niaziridin was discovered in the pods of moringa as compared to its leaves (Min Zhang, 2011). P-cymene, Moringyne, α-phellandrene are the most significant bioactive constituents established in the seeds of moringa (Ogunbinu et al., 2009; Shinde & Kamble, 2020), while the moringa pods are loaded with zeaxanthin, luteoxanthin, lutein and β-carotene. Isothiocyanate and glucotropaeolin derivatives are recognised from the seeds of *Moringa oleifera*, *Moringa peregrina* and *Moringa stenopetala* (Saini et al., 2016).

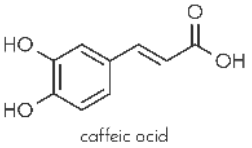
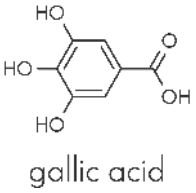
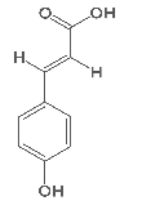
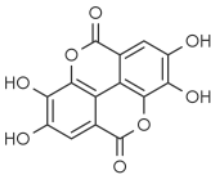
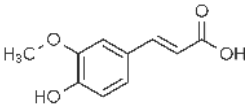
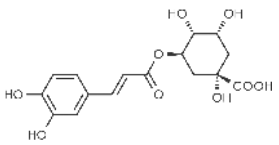
Among all parts of moringa, leaves are the most consumed part, which is loaded with vitamins, isothiocyanates, flavonoids, saponins, phenolics, carotenoids, tannins, glucosinolates and alkaloids (Leone et al., 2015). Total phenolic content (TPC) is extremely high in leaves contrasted with other plant parts. While gallic acid is a chief phenolic constituent found in moringa leaves, coumaric acid, chlorogenic acid, caffeic acid and ferulic acid also exist in the leaves (Bajpai et al., 2005; Min Zhang, 2011; Prakash et al., 2007; Singh et al., 2009). Sixteen flavonoids, including flavones and their derivatives, are discovered in dried or fresh leaves (Leone et al., 2015). Flavonoids, for instance, 6,8,3,5-tetra-methoxy apigenin and chrysoeriol 7-orhamnoside and the amyrin terpenes are exclusively established in leaves of *Moringa*

peregrina (Prakash et al., 2007). Moringa leaves consist of glucomoringin, sinalbin, two glucosinolates, together with isomers of benzyl glucosinolate. Moringa leaf extract has niaziminin, marumosides A, vincosamide and marumoside B as chief alkaloids, and lupeol as a mere single sterol. Further metabolites, for instance, benzene derivatives, niaziridin, niazirin, D-allose and niazirinin, are also found in the leaves of moringa. Gamma-sitosterol, nonacosane, octacosane and 1,30-triacontanediol were also established in the leaves with the help of a gas chromatography/mass spectrometry study. Beneficial phytates and oxalates are also found in the moringa leaves. Different studies have documented that greater contents of vitamins such as ascorbic acid, niacin, vitamin A, riboflavin, α-tocopherol and thiamine are established in the fresh moringa leaves. Sitosterol and its derivatives are established in the stem of *Moringa peregrina* and *Moringa oleifera*. Procyanidins and cryptochlorogenic acid are the chief bioactive constituents established in the moringa stem (Atawodi et al., 2010; Shinde & Kamble, 2020; Vongsak et al., 2014).

Leaves of *Moringa oleifera* are loaded with minerals, such as copper, iron, calcium, zinc, phosphorus, potassium and magnesium (Milla et al., 2021). One of the features of leaves is their high protein content because of EAA (essential amino acids), which makes up about 30% of their weight (similar to milk powder which comprises 35%) and is accessible all year round, as the content of essential amino acid and protein is found in the leaves, in contrast to other plants which contain them in the seeds (Amaglo et al., 2010; Milla et al., 2021; Olson & Fahey, 2011), meanwhile documenting 29.4 grams per 100 grams of protein in the dried leaves. Hence, *Moringa oleifera* can be considered a novel protein source to be added to food, similar to chia seeds with 24 grams per 100 grams of protein content in dry weight (Timilsena et al., 2017).

The leaves are renowned for high beta carotene levels and give more vitamin A in comparison with pumpkin and carrots (Ma et al., 2020), though it is unclear whether this vitamin continues to exist after drying and pulverising the plant. Studies have demonstrated that the consumption of this plant is enough to counteract the outcomes of vitamin deficiency (Olson & Fahey, 2011). Moringa plant is also a good vitamin B source, among which niacin, riboflavin and thiamine have been established, with concentration ranges between 0.8 and 0.82 mg/100 grams, 0.05 and 0.17 mg/100 grams and 0.06 and 0.6 mg/100 grams for niacin, riboflavin and thiamine correspondingly (Leone et al., 2015; Sánchez-Machado et al., 2006). On the contrary, 100 mg/deciliter supplementation of moringa leaf per day has an identical effect to treatment with 50 mg/deciliter of vitamin E per day (Ma et al., 2020). Moringa consists of more calcium as compared to dairy products and more vitamin C as compared to an orange, though a considerable part of calcium that is found in moringa is in the calcium oxalate form, which cannot be consumed by the human body and is directly excreted without being absorbed (Olson & Fahey, 2011). Moreover, *M. oleifera* is loaded in iron and potassium, even more than spinach and bananas, respectively (Milla et al., 2021). With reference to carbohydrates, the stem with bark consists of 31.1%; pods consist of 10.4%, bark consists of 26.9% and stem of 18.5% (Abdulkadir et al., 2016). Karuna et al. (Verma & Nigam, 2014) established that the root has the highest fibre level (45.43%) in contrast with bark (25.73%) and stem (41.60%). Immature flowers and pods are identified by a greater content of MUFA (monosaturated fatty acids), i.e. 16 to 30%, and are low in polyunsaturated fatty acids, i.e. 34 to 47%, in contrast with leaves (Saini et al., 2014) (Table 19.3).

Table 19.3 Phenolic Constituents Found in Moringa Leaves

Name of the constituent	*Chemical structure*	*Pharmacological uses*	*References*
Caffeic acid	 caffeic acid	Anticarcinogenic, antibacterial, antioxidant, cardio-protective and anti-atherosclerotic	(Greenwald, 2004; Magnani et al., 2014)
Gallic acid	 gallic acid	Antioxidant, anti-inflammatory, antimicrobial, gastro-protective and antineoplastic activities	(Choubey et al., 2015; Kahkeshani et al., 2019; Pandurangan et al., 2015)
P-coumaric acid	 p-Coumaric acid	Decreases TNF-α, anticancer, antioxidant, anti-inflammatory effects, enhances levels of serum antibodies, protects from UV-induced skin damage and skin ageing	(An et al., 2010; Boo, 2019; Pragasam et al., 2013)
Ellagic acid	 ellagic acid	Free radical scavenging effects, antibacterial, antimalarial, antioxidant, antifungal, anti-inflammatory, hepatoprotective, and anti-arrhythmic	(Bulani et al., 2015; Evtyugin et al., 2020; Savic et al., 2019; Soh et al., 2009)
Ferulic acid	 ferulic acid	Anticancer, antimicrobial, antidiabetic, anti-inflammatory, free radical scavenging effects, antioxidant, enhances angiogenesis and accelerates wound healing	(Zduńska et al., 2018)
Chlorogenic acid	 chlorogenic acid	Antioxidant, antimicrobial and anti-inflammatory	(Liang & Kitts, 2015)

Pharmacological Properties of Moringa

Anticancerous Properties of Drumstick

Almost 9.6 million people died of cancer globally, and cancer is considered the largest category of ailments (Siegel et al., 2020). Management of cancer is costly and includes radiation, surgery and chemotherapy, which are reported to have adverse effects. Research data have revealed that moringa/drumstick can be consumed as an agent that can work against neo-proliferation, in that way decreasing the cancer cells' growth. Moringa can be utilised as an agent with anticancer properties because it is safe, natural and reliable at accepted concentrations. Solvent and soluble leaf extracts have been shown to be efficacious as anticancer drugs.

Moreover, research studies propose that drumstick's antiproliferative activity on cancer is perhaps because of its capacity to persuade ROS in the cancer cells. Studies reveal that the ROS instigated in the cells give rise to apoptosis. This is further confirmed by the caspase nine and caspase three upregulation, a segment of the pathway for apoptosis (Gopalakrishnan et al., 2016).

Furthermore, the synthesis of reactive oxygen species by moringa is precise and attacks only cancer-causing cells, presenting it as the most suitable anticancer agent. Tiloke et al. (2013) also revealed that the extracts enhanced the glutathione-s-transferase expression, decreasing the antioxidant expression. Leaf extracts of moringa have been demonstrated to be anticancer and antioxidant agents which persuade reactive oxygen species. The leaves' constituents held accountable for the anticancer effects are benzyl isothiocyanate, glucosinolates and niazimicin (Hermawan et al., 2012). While benzyl isothiocyanate has been demonstrated to be associated with cancer, data from the research reveals that benzyl isothiocyanate causes reactive oxygen species inside the cells to grow, giving rise to cells' death. This could be among the causes for moringa to act as a fine anticancer herb (Gopalakrishnan et al., 2016).

The reduction in the ability of cancer cells to work successfully could be because of the phenolic constituents, particularly isopropyl isothiocyanate, D-allose and eugenol. Eugenol plays a considerable role in the MDAMB231 (breast cancer cells) apoptosis by means of the Bax protein overexpression; it may also provoke apoptosis by means of the E2f1/survivin downregulation in cancer cells of the breast. The hydroxycinnamic acid and hydroxybenzoic acid derivatives in leaf extract of *Moringa oleifera* could have a potential role in managing and preventing cancer, as stated in numerous studies. The in silico and in vitro outcomes revealed that 4-hydroxy 3-methoxy cinnamic acid, quercetin, P-coumaric acid and gallic acid demonstrated strong anticancerous properties and fine treatment potential against the malignant tumour (Mumtaz et al., 2021).

Moringa as Bone-Protective Agent

Osteoporosis is a compound disease affected by several environmental and genetic factors. It causes the bone mass to decrease and structural damage to the tissue, giving rise to skeletal weakness and chances of fracture, making the patient's life difficult. Osteoporosis emerges because of bone integrity loss which predominantly relies on intricately coupled osteoclastic resorption of bone and osteoblastic bone formation activity (Patel, 2013).

Over the past 20 years, several studies have been issued describing *Moringa oleifera*'s role as a strong pharmaceutical candidate, one of which was discussing its bone-protecting effects in female Wistar rodents who have had one or both ovaries removed surgically (Burali et al., 2010). Another study by Vali and coworkers (Vali et al., 2007) demonstrated that specific flavonoids could have a constructive effect on in vitro bone nodule development. As *Moringa oleifera* is loaded with particular flavonoids, they might be responsible for causing a substantial role in revitalising osteoblastic cells. One more study conducted by Rangrez and his colleagues (Rangrez et al., 2011) revealed that *Moringa oleifera* protects against the loss of bone caused by ovariectomy, though whether it encourages bone formation or protects against bone loss was not well established (Patel, 2013).

Anti-Inflammatory and Wound-healing Properties of Moringa

Increased levels of pro-inflammatory indicators are associated with chronic diseases such as type 2 DM which is an outcome of metabolic disorder (Graves et al., 2007). Patients with diabetes show increased levels of interleukin-6 and tumour necrosis factor-α while giving rise to the development of macro- and microvascular changes, which is a feature of patients having diabetes. The pods and seeds of moringa have been emphasised in lots of research studies for possessing anti-inflammatory activities (Araújo et al., 2013; Cheenpracha et al., 2010; Muangnoi et al., 2012). The moringa root extracts were stated to have intense anti-inflammatory activities in a carrageenin-persuaded paw oedema experiment in rodents (Sulaiman et al., 2008; Udupa et al., 1994). An analysis of the bark stem extracts having immunity-modulating properties on monocytic cells of humans (THP-1) demonstrated considerable reduction of IL-6, IL-1 and TNF-α, as well as the synthesis of NO (nitric oxide) and ROS (reactive oxygen species) (Vasanth et al., 2015). Ethyl ester, eicosane, N-hexadecanoic acid, β-sitosterol, Cis-13-octadecenoic acid, dodecane, methyl ester, hexadecane, benzoic acid, heptadecane and hexadecanoic acid are a few of the metabolites recognised in seeds, root and leaf of *M. oleifera* (Chuang et al., 2007; Faizi & Hussain, 2014; Leone et al., 2015), several of which are identified as showing anti-inflammatory properties (Bhandari et al., 2014; Pandith et al., 2013; Valerio & Awad, 2011).

Antidiabetic Properties of Moringa

Diabetes mellitus continues to exist as a chief health concern for the public. It is a metabolic disorder having numerous causative agents distinguished by persistent high blood glucose ensuing from imperfections in secretions or activity of insulin or both. In diabetes mellitus, high blood glucose has been related to the enhanced synthesis of inflammatory mediators and reactive oxygen species (Ansari & Dash, 2013; Omodanisi et al., 2017). In one of the reports by the IDF (International Diabetic Federation), it was documented that more than 246 million people were suffering from diabetes, and the frequency is anticipated to increase to around 380 million around the globe by 2026 (Malviya et al., 2010). Numerous medicines have been invented for the management of diabetes. However, there are restrictions on

the consumption of antidiabetic drugs because of their adverse effects, restricted mechanism of action, secondary failure and raised costs (Baggio & Drucker, 2007). Several plants and their parts are being analysed by researchers for their antidiabetic effects. *Moringa oleifera* is one of these plants; its leaves were stated to considerably reduce the concentration of blood glucose in diabetes models of Goto-Kakizaki and Wistar rats (Ndong et al., 2007). Other research studies also specified the potency of *Moringa oleifera* to efficiently decrease the levels of blood glucose (Kadir et al., 2012; Omodanisi et al., 2017).

Various research studies on animal models show that leaf extract of *Moringa oleifera*, when given orally, inhibits the development of fructose-persuaded diabetes. Further research studies demonstrate that powder of *Moringa oleifera* leaves mitigates alloxan-persuaded high blood glucose, showing its potential in the treatment of diabetes. These antihyperglycemic activities of *Moringa oleifera* were additionally shown in an animal experiment that demonstrated water-based extract of *Moringa oleifera* leaves harmonising streptozotocin and diet-induced hyperinsulinemia and hyperglycemia (Tshabalala et al., 2019). Jaiswal et al. (2009) analysed the fluctuating doses of water-based *M. oliefera* extract for their antidiabetic perspective on mildly and intensely persuaded diabetic rodents. Reduced glucose levels (29.9%) were reported from normal rodents given 200 mg/kilogram of drumstick. In extremely diabetic rodents, blood glucose levels were brought to almost regular levels with a drop of 51.2% and 69.2%. An accompanying improvement in levels of haemoglobin and total protein was also documented after 21 days of treatment with *Moringa oleifera*, therefore favourably inhibiting diabetes (Jaiswal et al., 2009; WHO Study Group on Prevention of Diabetes Mellitus, 1994).

In one of the studies, the blood glucose–reducing effect of moringa extract was established to be comparatively identical to an antidiabetic medicine (Glipizide). This investigational verification further proves the claimed potential of moringa extracts in treating diabetes (Tshabalala et al., 2019). The powder extract of *Moringa oleifera* fruit consists of N-benzyl carbamates, N-benzyl nitriles, a benzyl ester and benzylthiocarbamates which were documented to have intensely provoked the generation of insulin in the pancreatic β-cells of rodents. The secreted insulin had cyclooxygenase enzyme and lipid peroxidation–reducing properties. The utilisation of water-based extract of moringa leaves for more than eight weeks of duration re-established all the alterations (lipid profile, body weight, insulin and plasma glucose) to around regular or near regular in rodents suffering from type 1 diabetes. Glucose tolerance improved by means of using supplementation of *M. oleifera* over prolonged periods has also been documented (Tshabalala et al., 2019).

Anti-Infective Properties of Moringa

The phenolic constituents have been related to the antifungal and antibacterial activities of moringa extracts (Tesfay et al., 2017) one of the studies revealed this property of leaves against fungal infections such as *Trichophyton mentagrophytes* and *Trichophyton rubrum* (Milla et al., 2021). The moringa roots have antimicrobial properties and are reported to be loaded with antibacterial agents. While the bark extract has been established to have antifungal activities, both the stem and bark juice demonstrate antimicrobial activity against *Staphylococcus aureus* (Khor et al., 2018).

Hepatoprotective Effects of Drumstick

Moringa oleifera or drumstick plays a considerable role in protecting the liver from toxicity, oxidation and destruction because of the high quantity of polyphenols in its flowers and leaves. Oil of *Moringa oleifera* can also reinstate hepatic enzymes to regular levels, decreasing oxidative stress and enhancing protein content in the liver. The roots and flowers of the moringa plant consist of a constituent known as quercetin, which is identified to have protecting effects on the liver (Milla et al., 2021). Other constituents enclosed in the plant with hepatoprotective activity are glycosides of quercetin, β-sitosterol, flavonoids and rutin (Mahajan & Mehta, 2011; Panda et al., 2013), which also avert the oxidation of lipids (Shah et al., 2015).

The leaf extract of *Moringa oleifera* demonstrated wonderful effects against a range of cancer-causing cells (Al-Asmari et al., 2015). Balamurugan et al. (2014) reported the antitumour activity of moringa extract against HepG2 (cell line of hepatic carcinoma). The plant chemicals revealed an effective role in the prevention and management of cancer by impeding cancer cells by means of stimulating enzymes and hormones, increasing the synthesis of defensive enzymes that encourage antioxidant activity and increase immunity (Dalasanur Nagaprashantha et al., 2018; Kaleo et al., 2019; Smitha Grace et al., 2019).

Antihyperlipidemic Effects of Moringa

One of the studies by Divi et al. (2012) states that aqueous leaf extracts of *Moringa oleifera* showed strong antihyperglycemic and antihyperlipidemic properties in both type 1 and type 2 diabetic rodents. The leaves of *Moringa oleifera* consist of bioactive plant chemicals such as β-sitosterol with cholesterol-reducing effects. This constituent can decrease cholesterol levels in the blood of high-fat-diet-fed rodents (Farooq et al., 2012). Another study (Mehta et al., 2003) stated that the *Moringa oleifera* fruits were stated to have hypolipidemic activity. They were established to decrease the serum LDL, phospholipids, VLDL, the ratio of cholesterol to phospholipids, triglycerides, atherogenic index and serum cholesterol in hypercholesterolemic rabbits; however, they were established to enhance the ratio of high-density lipoprotein when contrasted with the control groups (Mehta et al., 2003).

Safety Evaluation of Moringa

Even though there are lots of benefits of utilising *Moringa oleifera* for therapeutic reasons, its harmful effects are usually overlooked. There are some propositions that in humans, it can't be consumed in a blend with other contemporary medicines; for instance, anecdotal verification recommends that when managing thyroids, constituents of moringa leaf may assist in the functioning of the thyroid gland (Tahiliani & Kar, 2000). This verification further proposes that perhaps it can antagonise other medications of the thyroid gland and precipitate the interaction of medicines. It is believed that drumstick could negatively inhibit the hepatic breakdown of substances (Das et al., 2012; Kelly, 2000; Sileshi et al., 2014). In this respect, moringa could diminish the breakdown process for some drugs in the liver. This could lead

to hepatic failure or cirrhosis, ensuing in malnutrition and loss of weight, and simultaneously diminished cognitive function.

Additionally, drumstick has been observed to be a better insulin modulator (Gholap & Kar, 2004). Hence, patients suffering from insulin deficiency are restricted to having negative depletions in their levels of sugar when consuming *Moringa oleifera* for therapeutic reasons (Gholap & Kar, 2004; Sileshi et al., 2014); it is speculated that it could drop the blood glucose to even minimum levels when consumed in amalgamation with other contemporary drugs (Sileshi et al., 2014). Research conducted by Barichella et al. (2019) analysed the safety, appropriateness and consumption of *Moringa oleifera* in Zambian children. Concerning its safety, a 14-gram supplementation of *Moringa oleifera* powder per day was considered safe for adolescents and children both in the long and short term. Barichella et al. also observed that nausea was documented in around 20% of the children in different age groups when the foods were regularly supplemented with 20 grams of drumstick. The ethical board considered these adverse effects tolerable (Barichella et al., 2019). Comprehensively, the outcomes of studies underline the fact that despite the insufficient safety data on the consumption of *Moringa oleifera*, none of the scientifically established adverse effects of this plant has been reported to this date (Stohs & Hartman, 2015).

Conclusion

Moringa oleifera is a versatile plant with lots of nutritional and pharmacological activities; it can be called a superfood because it is rich in vitamins, minerals and essential plant chemicals. The minerals loaded in the moringa plant are indispensable for the growth and development of the human body. It also consists of the most beneficial plant chemicals, including flavonoids, tannins, alkaloids, terpenoids, saponins and anticancerous agents. It has strong anti-inflammatory, antidiabetic and antioxidant activities, because of which it is beneficial in preventing chronic disorders, cancer and several metabolic diseases. Taking the traditional and contemporary uses of moringa into account, it should be researched further to know its role in viral diseases and how it can help in boosting the immune system to combat various infectious diseases. Moreover, an individual constituent of the plant should also be trialled clinically to better understand its interactions with other conventional medicines and food.

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Chapter 20

Role of *Curcuma longa* and Its Constituents, Especially Curcumin, in Prevention and Management of Diseases

Introduction

There has been a history of turmeric usage in the culture of the Indian subcontinent for 4,000 years; it has been used in Asian countries for many decades not only as a flavour or spice but also for medicinal purposes. Traditional books and manuscripts of Ayurvedic and Greco-Arabic or Unani medicine mentioned the use of turmeric several times. One of the famous Ayurvedic compilations named *Sushruta Samhita*, written by Acharya Sushruta, advised the use of turmeric for alleviating the harmful effects of toxic food. Not only traditional medicine but modern medicine also is beginning to identify its significance as thousands of manuscripts and books have been published about *Curcuma longa* in the past 30 years. The published literature about turmeric has revealed its miraculous effects in numerous experiments on animals and people with multiple diseases.

Curcumin is the major active chemical compound in *Curcuma longa*, commonly known as turmeric, belonging to the *Zingiberaceae* family. The chemical composition of turmeric is composed of curcuminoids which include cyclocurcumin and three types of curcumin that are present in different percentages with 77% curcumin I, 17% curcumin II and 3% curcumin III (Lee et al., 2013). Different *Curcuma* species of distinct geographical locations have different chemical content of curcumin, probably due to hybridisation with other species, so it is very important to select the species with higher content of curcumin (Hayakawa et al., 2011). In 1815, curcumin (diferuloylmethane) was isolated by Vogel and Pelletier while its chemical structure

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(1,7-bis[4-hydroxy-3-methoxyphenyl]-1,6-heptadiene-3,5-dione) was validated by Lampe and Miłobędzka in 1913 (Ammon & Wahl, 1991; Zhou et al., 2011). Curcumin is a phenolic compound and, due to its numerous pharmacological activities, gains the worthwhile attention of researchers all around the world (Hayakawa et al., 2011; Maheshwari et al., 2006). Turmeric has been conventionally used as a spice for a number of remedies for centuries (Araújo & Leon, 2001; Zhou et al., 2016). The Food and Drug Administration (FDA) generally recognise the safe dosage (GRAS) of up to 12 grams per day for healthy consumption without causing any side effects in human clinical trials (Gupta et al., 2013; Lao et al., 2006) (Figure 20.1).

Pharmacological Actions of *Curcuma longa*: A General Perspective

Numerous research articles show a broad-spectrum range of pharmacological activities including anti-inflammatory, antioxidant, antiseptic, analgesic, antimicrobial, antifungal, antiviral, antimalarial, anticarcinogenic, chemopreventive, pro-apoptotic, antiparasitic, hepatoprotective and chemotherapeutic activity possessed by *Curcuma longa* due to the chemical compound curcumin present in it (Çıkrıkçı & Mozio, 2008). Furthermore, strong evidence suggests the immunomodulatory potential of the spice curcumin. It has been found that curcumin regulates the activation of B cells and T cells, macrophages, natural killer (NK) cells, neutrophils and dendritic cells (DCs), as well as the secretion of immune cytokines in the human body (Ahmed et al., 2015; Momtazi et al., 2016; Cundell & Wilkinson, 2014; Seyedzadeh et al., 2014). Table 20.1 shows the description of some of the pharmacological properties of curcumin

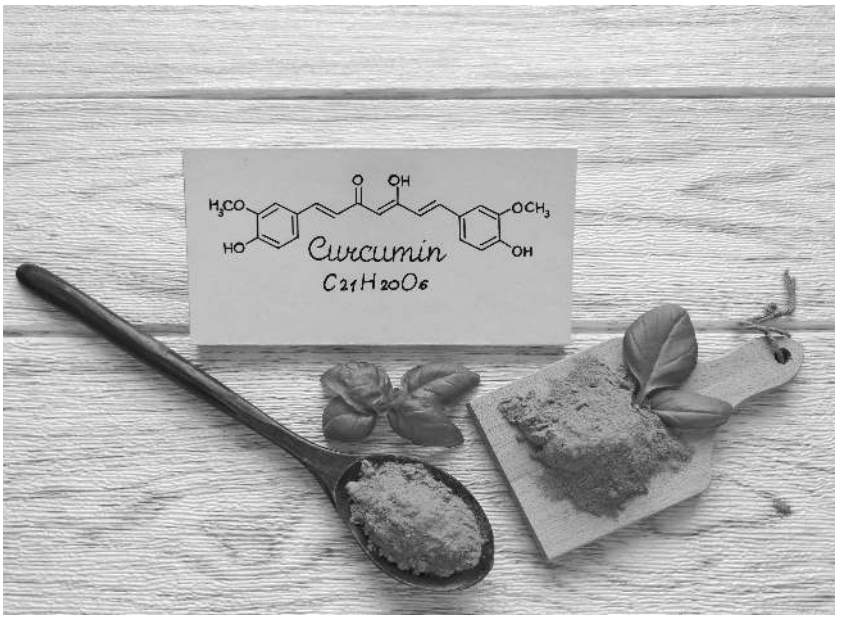

Figure 20.1 Chemical structure of curcumin along with turmeric powder.

Table 20.1 General Description and Activities of Curcumin

S. no		*Pharmacological activity*	*Description of function*	*References*
1	Antibacterial	*S. epidermis, Klebsiella pneumoniae, E. coli, Bacillus subtilis, Staphylococcus aureus*	Prevents bacterial growth	(Niamsa & Sittiwet, 2009)
		Vibrio, Bacillus, Salmonella, Staphylococcus and *Helicobacter pylori* species	Acts on the bacterial cell membrane	(De et al., 2009; Tyagi et al., 2015)
2	Antifungal	*Candida*	Inhibition of candida species' adhesion to human buccal epithelial cells (BEC)	(Martins et al., 2008)
			Develops magnetic interaction, which is hydrophobic with the cell membrane and creates a disturbance in the cell wall of fungi	(Kumar et al., 2014; Peters et al., 2010)
3	Antiviral	Parainfluenza virus type 3 (PIV-3), respiratory syncytial virus (RSV), feline infectious peritonitis virus (FIPV), vesicular stomatitis virus (VSV), flock house virus (FHV)	• Inhibition of haemagglutination • Inhibition of virus aggregation and replication	(Mathew & Hsu, 2018)
		Enterovirus	Inhibition of viral replication	(Qin et al., 2014)
		Herpes simplex virus (HSV)	• Reduction of HSV-1 replication • Significant protection in a mouse model	(Flores et al., 2016)
		Hepatitis C virus	Inhibition of viral entry, suppressing the Akt-SREBP-1 pathway	(Kim et al., 2010)
		Human cytomegalovirus		(Lv et al., 2014)
		Chikungunia virus, Zika virus	Inhibition of virus	(Mounce et al., 2017)
		Ebola virus		(Baikerikar, 2017)
		Epstein-Barr virus		(Chen et al., 2009)
		HIV	Inhibition of HIV	(Nekhai et al., 2015)

(*Continued*)

Table 20.1 (Continued) General Description and Activities of Curcumin

S. no		*Pharmacological activity*	*Description of function*	*References*
5	Anticarcinogenic	Lung cancer	Activates DNA fragmentation	(Chen et al., 2014; Jin et al., 2015)
		Liver cancer	In human hepatocellular carcinoma, mitochondrial nucleic acid disruption is found by the use of curcumin	(Du et al., 2013; Marquardt et al., 2015)
		Colorectal cancer Pancreatic cancer Chronic myeloid leukaemia Prostate cancer Breast cancer	• Interferes with different biochemical routes involved in the proliferation of carcinoma cells • Suppression of NF-κB and STAT3 activation • Negative effect on metastasis of carcinoma	(Park, 2010) (Youns & Fathy, 2013) (Yu et al., 2013) (Cao et al., 2017) (Liu & Ho, 2018)

The Activity of Curcumin in Different Diseases

Curcumin is used in the treatment of different inflammation of organs and for immune-mediated diseases. Following are the description of a few diseases in which curcumin mediates the inflammatory cytokines and influences various features of the immune system in various diseases with immunological causes.

Role of Curcumin in Cardiovascular Disorders

The main features of atherosclerosis include long-term chronic inflammation and immune reaction. Few agents are present which are anti-inflammatory and are used for treatment in atherosclerotic conditions, like statins. Some inflammatory cytokines are also responsible for the disease's development and enhancement, which include elevated IL1β, TNF-α, MCP-1 and reduced IL-10 and TGF-β (St-Pierre et al., 2003). A study revealed that the oil of curcumin used in atherosclerotic patients showed a significant decrease in the expression of mRNA proinflammatory cytokines including TNF-α, IL-6, IL-1β and IFNγ, whereas an increase in IL-10 expression in peritoneal macrophages (Singh et al., 2015). Curcumin further decreased the endothelial progenitor cell proliferation and colony-forming capacity. IL-10 mediates the anti-angiogenic effects. In cardiac ischaemia and cardiac injuries, proinflammatory cytokines are released and reduce the anti-inflammatory activities. In such injuries, curcumin elevates the IL-10 level and provides protection (Yeh et al., 2005). In immunodeficient patients, protease inhibitor ritonavir is responsible for causing cardiovascular problems and vascular dysfunction due to oxidative stress, decreased levels of NO and increased oxygen production. Curcumin has the ability to block ritonavir's effects; the study significantly shows 71% vessel contraction, 59% endothelium-dependent relaxation and 52% endothelium-independent relaxation in comparison with the control group. It inhibits cardiovascular complications, and thus, it increases the life span of immunodeficient individuals (Chai et al., 2005).

Role of Curcumin in Neurological Disorders

Neurological disorders are generally developed by the neuroinflammation and activation of microglia cells of the central nervous system (CNS) in chronic immunocompromised individuals. Curcumin-bound nanoparticles successfully reduce neurological disorders by inhibiting Tat activated proteins and also suppress inflammatory cytokines NF-kb, TNF-α and IL-1β (Guo et al., 2013; Yu et al., 2018). Curcumin provides protection against 1-methyl-4-phenylpyridinium, which is responsible for causing inflammation in astrocytes and inhibiting the proinflammatory cytokines by enhancing IL-10 in Parkinson's disease (Yu et al., 2016). It further shows a neuroprotective effect against neuronal loss. It regulates the PI3K/Akt pathway and prevents the breakdown of synaptophysin and PI uptake in the hippocampus, which is important and favourable in Alzheimer's disease. Curcumin further reduces the level of inflammatory cytokines, including IL-6, by activating glial cells and enhancing the IL-10 level (Hoppe et al., 2013; Schmitt et al., 2020). Encephalomyelitis is another inflammatory autoimmune abnormal condition of the brain and spinal cord. A study revealed the use of curcumin as treatment by the up-regulation of IL-10 and

Treg cells in the central nervous system and lymphoid organs in experimental autoimmune encephalomyelitis (Kanakasabai et al., 2012).

Role of Curcumin in Gastrointestinal Disorders

Diarrhoea prevalence is up to 14% in immunocompromised patients. A daily dose of 1.86 gm of curcumin resolves diarrhoea in 13 ± 9.3 days. A study reported decreased abdominal pain and bloating complaints as well as a remarkable weight gain in a few patients, along with the resolution of diarrhoea after the use of curcumin (Conteas et al., 2009). Curcumin also showed significant results in Crohn's disease and is very useful in the treatment of colitis (Sánchez-Calvo et al., 2009). A study showed the positive results of curcumin and a 68% reduction of myeloperoxidase activity, and an increase of IL-10 by 400%. Low IL-10 and high levels of serum TNF-α and IL-12 concentrations were seen in induced colitis by trinitrobenzene sulfonic acid (Bastos et al., 2016). Similarly, low IL-10 with high Cox-2 levels are found in colonic carcinoma. Curcumin, in such cases, has the ability to increase IL-10 in the ileum, spleen and lymph nodes in the animal model of ileitis (Bereswill et al., 2010; Sonoshita et al., 2002). It also provides a protective effect against inflammatory bowel disease where innate and adaptive immune cellular functional disturbance is a known issue (Jia et al., 2010).

Anticarcinogenic Effects of Curcumin

A number of studies have been conducted which show the anticancerous activity of curcumin. Curcumin inhibits the growth of various cancers, including the brain, blood, breast, head and neck, gastrointestinal system, colon, liver, pancreas, ovary, prostate and skin cancers (Anand et al., 2008; Kunnumakkara et al., 2008). M2 macrophages are responsible for tumour formation, growth and progression, while M1 macrophages are there, which produce antitumour factors like IL-12. Their ratio is also a major indicator to evaluate the progression of the tumour. Curcumin markedly increases M1 whereas decreasing the M2 macrophages. In 2015 a study reported curcumin's significant activity for metastatic breast cancer by reducing IL-10 and increasing tumour cell apoptosis in mice (Shiri et al., 2015). Antitumour activity of curcumin is by preventing it from T cell reduction of tumours and increasing IFN-γ and IL-2, which are the major cytokines for T cell and cytotoxic T lymphocytes function and its formation. A daily dose of 3.6 gm of curcumin is suitable for the prevention of the malignant gastrointestinal condition. In immunodeficient patients, most B cell lymphoma is developed by the Epstein-Barr virus, while the study with curcumin reported inactivity of Epstein-Barr virus. Curcumin also enhances apoptosis in resting B cell chronic lymphocytic leukaemia (B-CLL), which inhibits the proliferation of Epstein-Barr virus and thus has significant results in carcinogenic conditions (Hayun et al., 2009).

Antidiabetic Effects of Curcumin

A hyperglycemic disorder, type II diabetes shows its inflammatory effects in the brain, heart, liver, kidneys and other organs. These inflammatory effects are due to inflammatory cytokines, transcription factors and different enzymes (Moller &

Berger, 2003). The neuroprotective and nephroprotective pharmacological properties of curcumin are significantly proven in various studies. In diabetes, the proinflammatory cytokine secretions increase, which mediates the adverse effects of angiotensin-converting enzyme (ACE) activation and angiotensin II (AngII) formation (Molina-Jijón et al., 2016). TNF-α, which is a proinflammatory cytokine, is always found high in the plasma of diabetic patients (Lampropoulou et al., 2014; Pavkov et al., 2015). Curcumin has the ability to decrease blood glucose levels and activate PPAR and antioxidant activity (Nishiyama et al., 2005). Anti-inflammatory activity of curcumin reverses disorders that are linked with obesity in type 2 diabetes, a study reported in mouse models. Curcumin also reduces lipid peroxidation and regulates hepatic enzymes, helping to increase plasma insulin levels (Murugan & Pari, 2007). A study showed a low level of IL-10 in diabetes mellitus patients in comparison with the control group. Furthermore, studies reported that a decreased level of IL-10 in blood serum had been linked to being deficient in glycemic control and continuation of the disease (Li et al., 2016). The highly protective effects of curcumin on kidneys and their functions as well as on the nervous system are regulated by the inhibition of ACE and AngII, which ultimately decreases the inflammatory mediators, especially TNF-α. Curcumin increased the serum level of IL-10 in diabetic patients and reduced their adverse effects (Abd Allah & Gomaa, 2015). Microvascular complications and neuropathic pain in diabetes have been attenuated by curcumin in mouse models reported in a study (Sharma et al., 2006).

Role of Curcumin against Acquired Immunodeficiency Syndrome

HIV is responsible for causing acquired immunodeficiency syndrome (AIDS) in advanced cases (Douek et al., 2009), while it can also cause numerous infectious diseases in the body. Antiretroviral therapy is considered to be the best HIV management, but yet the therapy is not clear, and for the wide range of benefits, alternative therapy is also advised along with it. Curcumin is one of the natural agents that is easy to access, cost-effective, has no reported adverse effects and is safe for use (Prasad & Tyagi, 2015). Curcumin loaded with apo transferrin capsulated in nanoparticles binds to transferring receptors, causing the cellular uptake and cytotoxicity of T cells, eventually inhibiting HIV replication. It also inhibited the expression of topoisomerase II a, IL-1b and COX-2 HIV-induced inflammatory activities (Gandapu et al., 2011). Curcumin inhibits proteases of HIV-1 and HIV-2 and integrase activity of HIV-1. It has an anti-inhibitory effect on the protein kinase pathway in numerous cells which ultimately prevents HIV and also other chronic conditions (Dong et al., 2014; Prasad & Tyagi, 2015).

Role of Curcumin against Arthritis

Rheumatoid arthritis (RA) is known to be a systemic inflammatory disease. Inflammatory cells, including neutrophils, high levels of inflammatory cytokines, C-reactive proteins and increased ESR levels play a major role in the pathogenesis of rheumatoid arthritis (Choy & Panayi, 2001). A 23 mg/kg/day dose of curcumin, when induced in rats, gives significant results in decreasing the cytokines like IL-1β, chemokines like MCP-1 and an oncogene which is related to the growth. Curcumin

has the ability to prevent synovial fluid inflammation and has anti-granulomatous activities (Funk et al., 2006). It provides significant results for osteoarthritis of the knee joint (Panahi et al., 2014). Fifty μM of curcumin can protect chondrocytes of humans against inflammatory cytokines, i.e. IL-1β-induced inhibition of type II collagen and β1-integrin expression, while regulating the caspase-3. In degenerative joint disease, the anti-inflammatory activity of curcumin helps in the reduction of cartilage breakdown (Shakibaei et al., 2005).

Role of Curcumin against Allergic Rhinitis and Asthma

Allergy and asthma are inflammatory conditions that are mediated by inflammatory cytokines; there is a major role of exotoxin, MCP-1 and MCP-3 in their pathophysiology. During a bronchopulmonary allergic response, IL-10 decreased TH2 cell actions that are reported in the mouse model, whereas in the patients with asthma, alveolar macrophages secrete IL-10 at a low level in comparison to non-asthmatic control group macrophages. Curcumin plays a significant role in clearing the congested airways and lungs and increasing the antioxidant level. A study evaluated the results of curcumin on IL-2, IL-5, granulocyte macrophage-colony stimulating factor (GM-CSF) and IL-4 by lymphocytes in atopic asthmatic patients. Results markedly inhibit the IL-5, GM-CSF and IL-4 production and indicate the potential abilities of curcumin to reduce allergic responses and inhibit the inflammatory mediators like cytokines that affect the eosinophil and IgE formation (Kobayashi et al., 1997). Mast cell degradation is further activated by immunoglobin, especially IgE, which generates an allergic response. Here IL-10 induces the function of Treg cells, which suppress the production of IgE. Curcumin, for this system, significantly reduces the symptoms of allergic rhinitis by increasing serum IL-10 and decreasing IL-17, which is responsible for the severity of disease in asthma and for lung hypersensitivity (Ma et al., 2013).

Role of Curcumin against COVID-19

As curcumin harmonises the replication and the cellular events of SARS-CoV-2, it similarly manifests the pathophysiological events of COVID-19. Experimental evidence revealed the efficacy of curcumin in several ailments, including influenza, inflammatory disorders and coagulopathy, while promoting this medicinal spice as an immunity-boosting treatment for COVID-19. In silico investigations revealed the ability of curcumin to interact with viral proteins and inhibit viral replication, growth and proliferation of disease. It protects from cellular and organ damage by enhancing immune cell differentiation. Furthermore, it also improves the activity of other drugs against the virus (Soni et al., 2020). Concerning psychiatric illnesses, the most commonly observed in the COVID-19 pandemic were fear, stress and anxiety. Thus there was a dire need to be focused on the mental health of individuals (Tandon, 2020) by means of treatments and preventions, uptake of immunity-boosting fruits and significant herbal medicinal ingredients because there is a great potential in herbs and ancient spices to fight with COVID-19 and regulate the psychoneuroimmune (PNI) response. Psychological state, i.e. mental status and immunity of the individual in the pandemic, decided the outcome in numerous cases since mental health has a great impact on immunity while depression

negatively affects the outcome of any disease. In this pandemic, curcumin as an immunity booster significantly reduced the effects of disease and inflammatory cytokines. Basically, curcumin regulates the monoaminergic group that includes dopamine, glutamate, serotonin and noradrenaline, which ultimately reduce stress, anxiety and depression (Rajkumar, 2020; Zalachoras et al., 2020). The number of associated disorders in COVID-19 is also reduced by curcumin by decreasing the regulators like STAT3. Escalated levels of inflammatory cytokines weaken the immunity of the individuals (Liu & Ying, 2020), while curcumin enhances the haematopoietic differentiation of immune cells (Vishvakarma, 2014) and thus reduces the pandemic effects. Curcumin boosts immunity, acts as an excellent antidepressant and improves neurogenesis and hippocampus functioning (Soni et al., 2020; Zalachoras et al., 2020).

Conclusion

The remarkable effects of turmeric and its constituents are usually acquired by means of its consumption with food, even in minimum quantities for prolonged durations. In TCM, *Curcuma longa* is recognised as a liver and blood tonic; moreover, it helps to move 'chi' (*qi*) and alleviate pain in the body, specifically in the joints. Turmeric also aids in alleviating the inflammation, pain and soreness of muscles after exercise, hence increasing recovery and performance in dynamic people. Numerous phytochemical analyses have demonstrated remarkable constituents in turmeric along with strong therapeutic potential. Certain information about its safety, interactions, mechanism of action and efficient dose is required for the logical use of *Curcuma longa* and its constituents in the management of various diseases in humans.

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Chapter 21

Religious Aspects and Medicinal Uses of *Salvadora persica* (Miswak)

For Maintenance of Oral Health

Introduction

Miswak (*Salvadora persica*), generally identified in Urdu as '*peelu*' and in Arabic as '*arak*', belongs to the *Salvadoraceae* family. The term *Salvadora* was proposed by Dr Laurent Garcin, in 1749, in honour of a Barcelona apothecary, Joan Salvador Boscá. The word '*persica*' is employed to evoke Persia; meanwhile, the typical 'L' abbreviation refers to Carl Linnaeus (father of contemporary taxonomy) (Ahmad & Rajagopal, 2012). *Salvadora persica* is commonly identified as 'miswak' because it is the most familiar miswak source and is substantially consumed among the 182 plant species and utilised as chewing sticks all around the globe (Sofrata et al., 2011). Miswak is also recognised as *siwak*, *meswak*, *miswaak*, *siwaki* and *miswaki* in divergent Arabic vernacular and countries, which indicates a tooth rinsing stick. Whereas in English, miswak has been mentioned as the 'natural or organic toothbrush'. *Salvadora persica* is cut from one of its ends to form its tip afterwards; an uncovered end is then masticated to make and shape it as a brush (Aumeeruddy et al., 2018).

In the Islamic world, utilisation of miswak as a toothbrush is remarkably advised as a Sunnah regularly performed by the prophet Muhammad (PBUH) and his fellows to attain dental health, and the prophet highlighted the significance of utilising *Salvadora persica* (miswak sticks) for the cleanliness of the oral cavity (Riggs et al., 2012).

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For the past several years, the World Health Organization has encouraged developing countries to enthusiastically and willingly accept medicinal herbs as a supplementary asset to proliferate the success of health systems (Al-Attass et al., 2016; World Health Organization, 2013). Amid the evidence-based remedies, *Salvadora persica* is undoubtedly classified as a 'miracle twig' (Sabbagh et al., 2020). The fresh roots, leaves, and twigs of this tree can be mixed with the regular diet and then consumed or applied as traditional herbal medicine for cough, asthma, rheumatic disorders, scurvy, oral ailments and other diseases (Abhary & Al-Hazmi, 2016; Khatak et al., 2010). The utilisation of *Salvadora persica* begins in the pre-Islamic and Islamic periods since it was initiated by Islamic or Arabic societies as an antecedent of toothbrushes to cleanse the oral cavity and to encourage better hygienic conditions of mouth (Haque & Alsareii, 2015). The beneficial properties of miswak with respect to oral or dental health can be described by its mechanical activity if utilised for brushing the teeth besides its medicinal constituents. The bioactive components such as tannins in miswak reduce enzyme glucosyltransferase to lessen periodontal disorders and plaque, moreover, resins prevent dental caries (Al Bratty et al., 2020). Furthermore, the anti-inflammatory, antibacterial and antioxidant activities of *Salvadora persica* have been attributed to various identifiable constituents in its natural extracts, i.e. NaCl (sodium chloride) and K^+ (potassium), as well as saponins, salvadourea, salvadorine, silica, vitamin C and diverse minerals (Al Bratty et al., 2020; Mohamed & Khan, 2013).

Poor oral health has a significant effect on overall wellbeing and quality of life (Kassebaum et al., 2017). Various systemic and chronic ailments have been ascribed to abysmal oral health. Disorders like stroke (Shiraishi et al., 2018), diabetes (Nakamura et al., 2016), cardiovascular disorders (Kiswanjaya et al., 2017) and mental illness (Kisely et al., 2015) have recently been related to the outcomes of poor oral health, for instance, dental caries, persistent oral infections and periodontal disorders. It is substantially recognised that the maintenance of oral hygiene by means of regularly removing deposits of food and dental plaque is an essential factor in protection from deprived oral health. The usage of a toothbrush along with dentifrices (paste or powder for tooth cleansing) is among the fundamental way to maintain oral health. Other remarkable methods include dental floss and mouthwash (Van Leeuwen et al., 2017). Usage of herbal composition to constructively influence the health of the oral cavity was clearly seen in dental floss, dentifrices, periodontal chip and mouthwash. In numerous developing nations, natural ways of cleansing teeth are by using miswak, chosen and made from the roots, twigs or stems of a diverse range of plants and are yet being practised because of their simplicity, low cost and availability (Niazi et al., 2016). Cultural and spiritual elements also have an impact on the admiration of miswak in these regions (Owens & Sami, 2016). The practice dates back millennia in the Middle East, Africa, the Americas and Asia (Gurudath et al., 2012). In different cultures chewing sticks are recognised by various names, i.e. in Hebrew '*qesam*', in Arabic 'miswak', in Latin '*mastic*', in Japanese '*koyoji*' and in Aramaic '*qisa*' (Bos, 1993) (Figure 21.1 and Table 21.1).

Historical Background of Miswak

The precise derivation of teeth cleansing devices is unidentified. Though, from historical times and prior to the discovery of the contemporary toothbrush, cultured

Figure 21.1 *Salvadora persica* (miswak).

Table 21.1 Taxonomic Classification of *Salvadora persica* (Miswak)

Kingdom	Plantae
Phylum	Magnoliphyta
Class	Magnoliopsida
Order	Brassicales
Family	*Salvadoraceae*
Genus	*Salvadora*
Species	*Persica oleoides*

people have utilised some kind of cleansing devices to purify and maintain the health of their teeth. The earliest devices include the toothpick/tooth stick and the twig brush, wood mop, *siwak* or miswak (Hyson, 2003). Toothpicks have been discovered as early as prehistoric times; they have been uncovered along with other toiletry items in the earliest Babylonian city of Ur, which thrived in nearly 3500 BC (Hyson, 2003). In the second century BC, Alciphron, the Greek sophist, suggested the utilisation of a toothpick to wash out the 'fibrous residue' persisting between the teeth subsequent to meal consumption. The term '*karphos*' was used by Alciphron to define the toothpick, which signifies 'blade of straw'. The toothpicks prepared from *Pistacia lentiscus* (mastic tree) were used by the Romans (Hyson, 2003). The ancient predecessor of the contemporary toothbrush might be the fibre brush of Babylonian, known as the 'fibre pencil', 'fibre stick' or 'chew stick', which was utilised as early as 3500 BC. One end of this wooden stick was squashed to segregate the fibres to

around one-fourth of an inch. Arabian people term this instrument miswak or *sawik* (Wu et al., 2001; Hyson, 2003).

Prior to the advent of Islam, Arabian people used the root of *arak* (*Salvadora persica*) (Hattab, 1997). *Sawik* was utilised by the old Arabs to maintain the shining and whiteness of their teeth since shiny and white teeth were linked with attractiveness and beauty. One more potential rationale for its use is its involvement in spiritual purity. In the primaeval Islamic era, the miswak usage set off as a segment of a graceful and cultivated way of life (Bos, 1993), while the utilisation of *sawik* as a fundamental instrument for the maintenance of oral hygiene has been included in Islam as a fragment of spiritual practice (van Vuuren & Viljoen, 2006). Islam has provided a high status to the *Salvadora persica* (miswak), and its significance has been emphasised in numerous prophetic statements which are explained by various commentators. The prophet Muhammad (SAW) firmly advised the usage of *Salvadora persica* (miswak) and was himself a passionate promoter of its use.

In accordance with the Muslim narrators of prophetic description, the use of *Salvadora persica* was a regular practice of the prophet Muhammad (PBUH) after waking up, before sleeping, prior to and after meals, subsequent to entering the house, prior to the recitation of holy texts or prayers and during the fasting period. Since that time, miswak has been prominently attributed in hygienic constitutions or jurisprudence in Islam (Galletti et al., 1993).

Probably the spiritual or religious influence of miswak is the main reason for its common usage by Muslims of the entire world. Nowadays, both the contemporary toothbrush and the traditional miswak are commonly used in Muslim regions. Usage of *Salvadora persica* is prevalent in Saudi Arabia, and people of young ages from the KSA are extensively integrating traditional and contemporary approaches to oral hygiene (Al-Otaibi et al., 2004; Haque & Alsareii, 2015).

Salvadora persica *in Light of Prophetic Medicine*

It is reported in the Sahihain that:

> Every time when the prophet Muhammad (PBUH) awaken[ed] at night, he would purify his mouth with miswak.

Moreover, a person should not use miswak from the unrecognised or unidentified tree as it might be toxic for them.

Miswak, when used in moderation, will make the roots of teeth stronger, make the breath odourless, prevent plaque formation and polish the teeth. Miswak is also beneficial in preserving the health of the gastrointestinal tract (al Jauziyah, 2010).

Among several medicinal systems for healing, there is a specific type of therapeutic system recognised by the name of Islamic or prophetic medicine, which describes and follows the revelations of the prophet Muhammad (PBUH), sayings and practice of Muhammad (PBUH) related to the medical situations, as well as his mode of living which gave rise to immense interest among the community of scientists to discover how a person who was living in the desert could provide such tremendous statements on medicine and healing. These eventually led the researchers to conduct studies comprehensively, and it is astonishing that none of the statements given by the prophet Muhammad (PBUH) regarding healing is established to be contradictory to medical science (Bhikha et al., 2015; Hussain & Hussain, 2016).

As a matter of fact, Islam has emphasised the use of miswak for cleansing of the oral cavity. The religion of Islam teaches the significance of cleanliness for both physical and mental health, and hence introduced fundamentals of oral health and cleanliness by integrating it as a practice of religion or spirituality (Aumeeruddy et al., 2018). The significance of using miswak was underlined by the prophet Muhammad (PBUH), who imparted his knowledge and taught about Islam not merely by his statements but also by means of his actions. With regards to Arak (*Salvadora persica*), the prophet Muhammad (PBUH) said 'choose the black fruit (Arak's fruit) since it is the best' (Bukhārī & Khan, 1997). Moreover, Aishah (wife of the prophet Muhammad [SAW]) narrated that: 'Miswak cleanse[s] the oral cavity (mouth) and gratifies the God', specifying its role in oral hygiene. Furthermore, the prophet Muhammad (PBUH) used *sawik* (*Salvadora persica*) frequently: whenever he awakened from sleep, when he would step into his house and prior to offering prayer, which signified the prominence of its continual usage for splendid hygiene of the oral cavity (Nasā' ī et al., 2007).

In point of fact, the use of *Salvadora persica* was not merely practised by the prophet Muhammad (PBUH), but by all prophets prior to him (peace be upon them), signifying its utilisation as ancient as the beginning of humankind in the world (Aumeeruddy et al., 2018). Yet, during the final time of the prophet Muhammad (PBUH) prior to his death, Aishah (wife of the prophet Muhammad [PBUH]) masticated the *Salvadora persica* and then wiped the teeth of the prophet Muhammad (PBUH) with it (Bukhārī & Khan, 1997). This demonstrates how eager the prophet was to use the *sawik*. Furthermore, the *sawik* (*Salvadora persica*) should be used whenever the odour in the breath of an individual's mouth alters, whether this is due to consuming food with a potent odour or due to not drinking or consuming anything for a longer duration (Aumeeruddy et al., 2018).

Method of Using Miswak

The technique of using miswak has formerly been discussed by Al Sadhan and Almas (1999) Concisely, the length of the miswak should be suitable for better grips and uncomplicated to operate in a limited space without shattering it. The *sawik* twig should be cut freshly so that it is masticated conveniently and still remain loaded with dynamic phytoconstituents. Around 1 cm of the external layer from one side of the miswak twig is peeled off to demonstrate the internal bristles, which are subsequently masticated to make them squishy. The pointed end is then immersed in water, but not for a longer duration because it may give rise to the loss of useful phytoconstituents. Usually, there are two fundamental ways of holding a miswak: a five-finger or three-finger grip. It is preferable to grasp it with the right hand by placing the thumb below the miswak's head adjacent to the bristle, with the pinkie finger (fifth digit) beneath the other end, and the three other fingers on the topmost part of the miswak (Figure 21.2). In spite of that, it relies upon the choice of the consumer which technique is more convenient and easy (Al Sadhan & Almas, 1999).

The objective is to ensure a firm but regulated movement of the bristle inside the oral cavity so that all parts of the mouth are approached with considerable convenience and ease. The methods utilised for brushing are identical to those for a particular toothbrush. The bristle of the miswak is gently pressed upon the teeth and rubbed so as to clean the back and front teeth surfaces and the surfaces of the molar and premolar teeth for making sure that the bristles have passed through the

Figure 21.2 Method of holding miswak.

spaces between the teeth. All remaining parts should be gently brushed, including the palate, soft palate, gums, tongue and the internal surfaces of the lip and cheek. Subsequently, the tip of the bristle should be washed for a short duration to get rid of any debris, and the *sawik* twig should be placed in a washed and uncontaminated place (Aumeeruddy et al., 2018).

Phytochemical Constituents

Almost all parts (twigs, bark, root, fruits, seed, stem and flowers) of *Salvadora persica* have been evaluated; a comprehensive investigation of plant chemicals showed the presence of terpenes, carbohydrates, alkaloids, flavonoids, sterols, organosulphur compounds, glycosides and elemental sulfur, as well as small quantities of calcium, silica, fluoride, phosphorus and ascorbic acid (Aumeeruddy et al., 2018). Roots are loaded with benzyl isothiocyanate and salvadourea, which reveals antiviral activity against harmful viruses of the oral cavity such as HSV (herpes simplex virus) (Farag et al., 2021). Moreover, a great alkaloids content such as trimethylamine and salvadoricine was present in the roots (Al Lafi & Ababneh, 1995). Furthermore, pyrrole, pyrrolidine and piperidine derivatives have been separated from the twigs of SP, which are nitrogen-holding compounds (Galletti et al., 1993). Extracts of stems, twigs, and roots have been stated to consist of great quantities of salvadourea (Khalil, 2006). A number of alkaloids, for instance, trigonelline, theobromine and caffeine, were also present in the bark (Farag et al., 2017).

Nearly 2 to 12% of amino acids were established in the roots, while merely 1% was detected in the stem. The amino acid L-alanine is considered the principal amino acid with a proportion of 1 to 10%; overall nitrogenous constituents were also established in the roots at greater levels, varying from 3.2–5% in contrast with 2.86% in the stem.

The roots from both Saudi and Egyptian plant sources have produced two glucosinolates: sinigrin and glucotropaelin (Farag et al., 2021). Syringin, salvadoside, lignan, salvadoraside and liriodendrin glycosides were separated from the stem (Ohtani et al., 1992). Cyanogenic glycosides were also established (Khalil, 2006). A raised percentage of 5-O-caffeoylquinic acid and naringenin is present in the bark (Farag et al., 2017). Seeds, roots and stems of *Salvadora persica* have been documented to consist of volatile constituents such as benzaldehyde, benzyl alcohol, tetradecanoic acid (Z)-9-octadecenoic acid ethyl ester, stearyl alcohol, Cis-2-methyl

cyclohexanol, amyl benzoate, 3-methyl-2-furan carboxylic acid, 3,4,5-trimethoxyphenol, N-acetyl piperidine, nonanal, elaidic acid, (Z)-9-octadecenoic acid, chloromethyl benzene, 3,5-dihydroxy-6-methyl-2,3-dihydropyran-4-one, tetradec-1-ene, hexadecanoic acid and pyridine derivatives, while the leaves' essential oils consist of thymol, β-caryophyllene, isothymol, eucalyptol, eugenol, benzyl nitrile and isoterpinolene as the chief constituents (Alali & Al-Lafi, 2003).

Medicinal Properties of *Salvadora persica*

Antimicrobial Therapy

Because of the fact that mechanical removal of damaged tissues and debris in the periodontal cavity and small areas does not perpetually kill all infectious agents, lingering infectious agents in the periodontal system frequently recolonise the areas of the periodontal cavity many weeks after treatment (Mombelli, 2018). Consequently, in addition to surgical and mechanical treatment, adjunctive usage of comprehensive chemotherapeutic antibacterial agents has been established to be more efficient in the extensive destruction of infection-causing bacteria (van der Weijden, 2019). In spite of the fact that systemic antibacterial treatment has numerous invigorating outcomes in periodontal management (Feres et al., 2015; Souto et al., 2018), it is generally reserved for cases with quickly developing or unmanageable periodontitis because of its major simultaneous drawbacks (Sahni et al., 2012).

The unforeseeable concentration of antibiotics at the targeted site, the possibility of an instant reduction in the concentration of plasma antibiotics lower than the suitable medicinal index and the evolution of resistance from antibiotics by microbes are merely a small number of these inadequacies (Feres et al., 2015; Sahni et al., 2012). Apart from that, introducing high systemic doses of antibiotics to a great number of cases may initiate a range of adverse effects (Feres et al., 2015; Sahni et al., 2012). Hence, the synthesis and exploration of confined intra-pocket medicine delivery systems for the management of the periodontal cavity were encouraged by the aforementioned prospective disadvantages of systemically given antibacterial chemotherapeutic agents (Mekhemar et al., 2021). This technique of confined distribution of medicine inside the periodontal pockets ensued in minimum adverse effects associated with medicines, greater doses of medicine at the intended site over extensive time periods and greater compliance of patients (Sahni et al., 2012). Local distribution of medicine for antimicrobial agents and other types of chemotherapeutic moderators in periodontal treatment can be obtained by the topical application of oral solutions and gels or by the administration of particular systems of delivery into periodontal areas, i.e. periodontal chips, for an extended release of the essential concentrations of medicines (Khatak et al., 2010; Mekhemar et al., 2021; Sahni et al., 2012).

Furthermore, contemporary approaches have demonstrated some microbial infectious agents are closely related to periodontitis, for instance, the classes of microorganisms, i.e. *Erysipelotrichia*, *Negativicutes* and *Clostridia* (Griffen et al., 2012), *Prevotella*, *Fusobacterium* (Costalonga & Herzberg, 2014) and *Synergistes* (Vartoukian et al., 2009); similarly the species *Aggregatibacter actinomycetemcomitans* (Ardila & Bedoya-García, 2020), *Methanosarcina mazeii*, *Methanobrevibacter oralis*, *Methanobacterium curvum/congolense* (Lepp et al., 2004; Matarazzo et al., 2011; Willis & Gabaldón, 2020) and *Filifactor alocis* (Griffen et al., 2012). Several studies have explained the antibacterial effects of *Salvadora persica* on different

kinds of microbes (Al Bratty et al., 2020; Arshad et al., 2021; Khalil et al., 2019). The products and extracts of miswak have been demonstrated to have considerable bacteria-killing activity against gram-negative and gram-positive microbes, as well as subduing microbial biofilms, in a lot of research experiments that encourage the usage of miswak as an antibacterial medicine in a range of ailments (Mekhemar et al., 2021). One of the suggested mechanisms of the miswak-facilitated bacterial killing function was focusing on the microbial membranes by BITC (benzyl isothiocyanate), which is one of the dynamic constituents of miswak extracts. Micrographs of periodontal infectious agents showed that complexes of benzyl isothiocyanate and miswak extracts might give rise to the membrane protuberances of bacteria like antimicrobial peptides (Socransky et al., 1998). By means of the disintegration of the external membrane of bacteria, bioactive complexes of *Salvadora persica* will invade the microbial cell and interrelate with the redox systems of the microbes, weakening the capability of the microbes to preserve their membrane potential. Such a method of benzyl isothiocyanate has also been documented for membranes of mitochondria (Socransky et al., 1998).

Another intended antimicrobial mechanism for miswak is the extended release of plant chemicals, i.e. β-Sitosterol, which have the prospective to subdue bacterial genotoxic substances accumulated on the teeth (Abhary & Al-Hazmi, 2016). Another study has established that when *Salvadora persica* is integrated with antibiotic drugs, it has a synergistic antimicrobial activity, revealing its function in microbial resistance repression (Saquib et al., 2019). All consequences demonstrated an extremely efficient bactericidal and inhibitory outcome of miswak extract on the experimented periodontal infectious agents, such as *Tannerella forsythia*, *Fusobacterium nucleatum*, *Aggregatibacter actinomycetemcomitans*, *Treponema denticola*, *Porphyromonas gingivalis* and *Prevotella intermedia*. The antimicrobial activity was stated to be in a dose- or time-reliant way with greater effects straight after the application of *Salvadora persica* (Albabtain et al., 2017), was found more effective in natural solvent extracts in contrast with aqueous extracts (Al-sieni, 2014; Saquib et al., 2019; Siddeeqh et al., 2016) and consisted of a coactive mechanism. It reported a greater sensitivity of miswak extract against gram-negative bacterial agents, particularly *Porphyromonas gingivalis*, as a predominant causative agent of periodontal disorder (Rafiei et al., 2017).

Anti-Inflammatory Effects of Salvadora persica

The stem extract of *Salvadora persica* has anti-inflammatory activity (Ezmirly et al., 1979). One of the studies (Alali & Al-Lafi, 2003) proposed that the *Salvadora persica* extract can be effectively utilised as an organic tool for cleansing teeth and as an organic pain-alleviating agent for managing toothaches (Haque & Alsareii, 2015). In experimental studies, the intensity of the inflammation in the gingiva can be measured by quantifying the altered GI (Gingival Index) (Safiaghdam et al., 2018). In numerous research studies, the Gingival Index was proposed as one of the secondary effects subsequent to plaque build-up. Saha et al. (2012) documented a considerably significant drop in the Gingival Index in the *Salvadora persica*–managed group contrasted to the modern toothbrush amid the cohort study conducted in Lucknow (Saha et al., 2012).

With respect to the mouthwash of *Salvadora persica*, Farhadian et al. (2015) and Sobouti et al. (2018) also incorporated the outcome of gingivitis in their study. Sobouti et al. (2018) documented a considerably better reduction of gingival inflammation by the mouthwash of miswak contrasted with the chlorhexidine amid their orthodontic cases, while another study reported a considerably better decrease of gingival inflammation by mouthwash of *Salvadora persica* in contrast with the intervention of electronic toothbrush among patients with confirmed gingivitis diagnosis (Farhadian et al., 2015; Sobouti et al., 2018).

Salvadora persica has astringent, analgesic and anti-inflammatory activities, which makes it an efficient treatment for primary inflammatory disorders of gums. Moreover, it has been observed that people who were using miswak daily had a decreased toothache incidence contrasted with the users of the conventional toothbrush (Niazi et al., 2016).

Antifungal Properties

Studies of recent times have validated the fact that miswak has antifungal properties (Haque & Alsareii, 2015). One of the studies contrasted the antifungal property of pulverised particles of miswak with solid miswak against various candidal strains. It was determined that solid miswak showed potent antifungal activity while ground miswak demonstrated no antifungal effects (Alili et al., 2014; Haque & Alsareii, 2015). Likewise, an in vitro experiment by Naeini et al. discovered that alcoholic extracts of miswak demonstrated antifungal properties against all candida strains except *Candida krusei* and *Candida parapsilosis* (Naeini et al., 2014). Moreover, the hexane constituents in the miswak roots were found potent against *E. faecalis* and *C. albicans* (Niazi et al., 2016).

Various Oral Products of *Salvadora persica* and Their Proven Effects

Miswak Mouthwash

Mouthwash has been identified as an efficient way to inhibit plaque (Farook & Said, 2018). The cationic chemical, chlorhexidine, frequently utilised in typical mouthwash because of its potential against oral plaque, has been stated to give rise to numerous adverse effects, for instance, the mucosal annoyance of the oral cavity, discolouration of teeth and unpleasant taste subsequent to its use (Marion et al., 2013). In consequence, the exploration for an organic alternative for mouthwash preparation was the need of the hour. A double-blind, randomised controlled trial was conducted by Niazi et al. (2018) to contrast the effectiveness of cetylpyridinium chloride, *Azadirachta indica* (neem), *Salvadora persica* and chlorhexidine on the inhibition of plaque among 80 patients who had gone through orthodontic management. Mouthwash prepared with *sawik* showed remarkably considerable reduction of plaque contrasted with two chemical agents. A mouthwash of *Azadirachta indica* could not show any considerable plaque reduction when contrasted with two chemical agents (Niazi et al., 2018). One more study compared chlorhexidine and miswak

mouthwash with reference to the status of plaque after orthodontic mediation also didn't notice any dissimilarity among the groups. The research was a single-blind (randomised controlled trial) study of 54 patients who had orthodontic management for four months. The reduction of plaque in both chlorhexidine and miswak groups was consequential in contrast with placebo mouthwash, proposing that *Salvadora persica* can act as a substitute for chlorhexidine (conventional chemical agent) in orthodontic patients (Nordin et al., 2020).

Miswak Toothpaste

Research revealed that *sawik* (*Salvadora persica*) has anti-inflammatory and antimicrobial activities, and its application in the oral cavity as toothpaste or mouthwash has been suggested (Haque & Alsareii, 2015). Toothpaste of *Salvadora persica* was remarkably more efficient in decreasing *Lactobacilli* than conventional toothpaste verified either instantly or after using for 14 days, and it might be that the potent antimicrobial activity of miswak is accountable for this effect (Naseem, 2014). This is in accordance with the outcomes documented by other research studies (Al-Dabbagh et al., 2016). Toothpaste of miswak was considerably more efficacious in decreasing *Streptococcus mutans* as compared to conventional toothpaste both instantly and after 14 days of use, which is also ascribed to the antimicrobial effects of *Salvadora persica* (miswak) (Al-Dabbagh et al., 2016; Naseem, 2014).

Poureslami et al. (2007) suggested the utilisation of miswak extract in toothpaste and mouthwashes because of its outstanding antibacterial outcomes. The study consisted of the outcomes of three in vitro studies that experimented with the effect of miswak extract on isolated microbial strains, contrasted with the para-clinical outcomes of Iranian toothpaste consisting of *Salvadora persica* extract and placebo toothpaste on a plaque in the dental cavity, and contrasted the antimicrobial effect of penicillin and a Swiss toothpaste with that of the Iranian (miswak extract) toothpaste in the dental plaque. (Halawany, 2012; Poureslami et al., 2007).

Miswak Chewing Sticks

Regarding comparing toothbrushes with miswak sticks, two of the research studies (Malik et al., 2014; Saha et al., 2012) also incorporated the outcomes of gingivitis in their research. Malik et al. (2014) documented no considerable variations concerning the reduction of gingival inflammation between a regular toothbrush and a chewing stick of *Salvadora persica*, whereas Saha et al. (2012) stated considerably higher inhibition of gingival inflammation in the *Salvadora persica* group contrasted with regular toothbrush among the cohort study conducted in Lucknow (Nordin et al., 2020). Otaibi et al. conducted a randomised controlled trial (single-blind) by including 15 participants from Saudi Arabia; the research showed that the impact of miswak stick upon the subgingival plaque microbes was identical to that of daily brushing of teeth without paste and that *Aggregatibacter actinomycetemcomitans* levels were considerably more decreased by utilising *S. persica* than by the brushing of teeth (Al-Otaibi et al., 2004) (Table 21.2).

Table 21.2 Research-Based Studies Proving the Oral Health Benefits of *Salvadora Persica* and Its Products

Type of study	*Compound used*	*Outcomes of study*	*Dosage form (if described)*	*References*
In vitro study	Yarrow, miswak and mint	Demonstrated weaker effect against *Aggregatibacter actinomycetemcomitans* but potent activity against *Porphyromonas gingivalis*	6% herbal solution versus chlorhexidine versus distilled water (sterile)	(Sofrata et al., 2011)
Randomised controlled trial	*Salvadora persica*	Considerable improvement of gingival status and plaque with oral drops of *Salvadora persica*	Chlorhexidine mouthwash with 10 drops of *Salvadora persica* or normal saline (15 mL) twice a day	(Bahrololoomi et al., 2020)
Triple-blind controlled trial	Triclosan polymer and fluoride-containing toothpaste and miswak toothpaste	The toothpaste that consisted of miswak revealed considerably greater reduction of plaque index contrasted with the modern toothpaste	Toothpaste	(Gupta et al., 2012)
Randomised controlled trial (single-blind)	Miswak versus chlorhexidine versus placebo	a) Plaque index was considerably decreased with both SP and chlorhexidine mouthwashes contrasted with placebo b) While the gingival index was considerably decreased with miswak mouthwash contrasted with placebo	Mouthwash	(Sobouti et al., 2018)
Randomised control trial (double-blind)	940 mg/ml aloe vera and 10 mg/ml *Salvadora persica*	a) Decreased gingivitis among intubated patients in intensive care units b) Significant reduction in gingival index contrasted with chlorhexidine	Mouthwash	(Rezaei et al., 2016)
Randomised controlled trial (single-blind)	Toothpaste of tea tree oil and *Salvadora persica*	Application of *Salvadora persica*/miswak toothpaste showed a considerably better plaque reduction than tea tree oil toothpaste	Toothpaste	(Varma et al., 2018)
Single-blind, randomised crossover study	Miswak stick vs toothbrush	Miswak considerably decreased the quantity of *Aggregatibacter actinomycetemcomitans* in the subgingival plaque	Miswak stick	(Al-Otaibi et al., 2004)

Safety Evaluation of Miswak

Toxicological studies have been carried out on root extract of *Salvadora persica* in animal models (Ibrahim & El-Gengaihi, 2012). Rodents were given up to 5 grams per kg of *Salvadora persica* intraperitoneally, and the safety of miswak was evaluated. No death rate or any noticeable sign of toxicity was observed for up to one week with 3 grams per kg of the *Salvadora persica* extract, while LD50 was established to be 4 grams per kg. Root extracts of *Salvadora persica* were established to be harmless for the kidney and liver as described by haematological and biochemical variables at a dosage of 400 mg per kg of body weight, though extracts revealed a negative impact on sex hormones by inhibiting testosterone and enhancing oestrogen secretions in male rodents. While on the contrary, levels of progesterone were inhibited in a female group of rodents. Another research carried out on dental stem cells of humans (Tabatabaei et al., 2015) discovered that water-based extracts of *Salvadora persica* revealed a cytotoxic effect at 5.75 mg/ml concentration and gave rise to the considerable proliferation of cells at 0.08 mg/millilitre and 0.17 milligram/ml after 48 hours. However, alcoholic extracts demonstrated toxicity following 28 and 48 hours. Moreover, another in vitro study explored the impact of *Salvadora persica* extract on fibroblasts of human gingiva (Balto et al., 2015). One mg/ml hexane extract of miswak demonstrated cytotoxicity in around 14% of the cells utilising assay of lactic dehydrogenase while assay crystal violet revealed toxicity in around 12% of cells. The greatest cytotoxicity was observed in the ethyl acetate-based *Salvadora persica* extract as the endurance of the cell was merely 66 and 40% when analysed by crystal violet and lactate dehydrogenase assay correspondingly. In an experiment to check for acute toxicity (of the oral cavity) within animal studies, 300 and 500 mg per kilogram concentrations of *Salvadora persica* were identified to be harmless in up to 5 grams per kg weight of the animal and mentioned no adverse effects following the administration of drugs (Ahmad et al., 2011).

Conclusion

Several research studies have been carried out to analyse the functions of *Salvadora persica* in numerous fields of dental science. *Salvadora persica* consists of a broad range of prospective management properties in numerous conditions of the oral cavity. Apart from its anticancer effects, it plays a remarkable role in preventing and managing different periodontal ailments and is proven by a range of analytical and research studies. Currently, there has been a surge in interest in natural medicines and their products as a substitute for modern medicines, and the disorders of the buccal cavity are no exception. On the other hand, many studies have demonstrated that miswak is equal to or better than a number of antibiotics consumed extensively to manage periodontal diseases. Moreover, several in vivo and in vitro analyses have stated noticeable benefits of utilising miswak to manage periodontal or gingival inflammation.

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Chapter 22

Nutritional and Medicinal Benefits of *Ficus carica*

Introduction

Ficus carica, commonly recognised as 'fig', is a small deciduous plant native to the Mediterranean region, Persia, Asia Minor and Syria. Fig belongs to the Moraceae family, which consists of one of the principal genera of angiosperms with around 800 species of creepers, shrubs, climbers, trees and hemiepiphytes in the subtropics and tropical regions. Brazil, Greece, Egypt, Turkey, California, Morocco, Italy and Spain are key producers of figs. Fig leaves are traditionally used to treat gingivitis, vitiligo, asthma, diabetes, constipation and cough. In contrast, roots are consumed for the management of ringworms and leukoderma. The fruits of figs also demonstrate purgative, anti-inflammatory, antipyretic, aphrodisiac and antiparalytic properties (Frodin, 2004; Rahmani & Aldebasi, 2017).

Fig is an ancient tree and has been growing for a very long time in the history of humans. The nutritious and beneficial values of *Ficus carica* are also stated in holy books such as the Bible and the Holy Quran. It consists of almost 15 anthocyanin pigments; the most common among them are pelargonidin derivatives, cyanidin and aglycone. Numerous volatile constituents such as bergapten, linalool, benzyl alcohol, eugenol, furanoid, caryophyllene, cinnamic aldehyde and angelicin are identified in the extract of the plant (Gibernau et al., 1997). The alcoholic extract of the plant has demonstrated antituberculosis and antipyretic activities (Khan, 2017; Patil et al., 2010).

Moreover, fig leaf extract has been shown hepatoprotective activities (Gond & Khadabadi, 2008). The latex part of the plant is stated to have antipathogenic activities against infectious agents in humans (Aref et al., 2010). Fig is consumed as a diuretic, expectorant and laxative in the Unani system of medicine. The desiccated fig fruit is identified to have antidiabetic properties, and the leaves are used to manage jaundice (Khan, 2017; Khare, 2004b, 2004a). In the Unani medicinal system, figs are used along with walnuts as an agent to enhance sexual pleasure, attraction

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Figure 22.1 *Ficus carica* (fig).

or desire. The fruit of *Ficus carica* is consumed either in dried, canned or raw form (Neal & Bernice Pauahi Bishop Museum, 1991).

The dried fig fruit is reported as a significant source of minerals, carbohydrates, phenolic constituents, vitamins and sugars (Jeong & Lachance, 2001; Slatnar et al., 2011; Veberič et al., 2008) while both dried and fresh fruit of the fig consists of polyphenols and fibre in high quantities. *Ficus carica* is a remarkable source of phenolic constituents such as proanthocyanidins; on the contrary, tea and red wine, which are two fine sources of phenolic constituents, consist of phenols in low quantities as compared to those in figs (Mawa et al., 2013). Its leaves, fruit and roots are consumed in traditional medicine to manage numerous disorders such as cough, sore throat, indigestion, diarrhoea, colic, bronchial issues, cardiovascular disorders, loss of appetite and as antispasmodic and anti-inflammatory agents. Moreover, it is commonly consumed in confectionary such as jellies, jams, desserts, cakes and *murabba* (preserved jams) (Khan, 2017; Duke & Duke, 2002; Werbach & Werbach, 1994) (Figure 22.1).

The Religious Importance of Figs

Tree as a metaphysical or holy object is not a novel concept, but the occurrence of figs amid this category is quite incredible. Numerous religions discuss trees and the unseen objects associated with them; while a number of them have no equivalent in the world, others are recognised as certain species, e.g. the 'tree of life' of Egyptians as the *Ficus sycomorus*, the 'sky tree' of Indians as *Ficus religiosa* and the mythic world in Hinduism with *Ficus benghalensis* (Eliade, 1987; Forlong, 1883; Hamilton, 2002). *Ficus benghalensis* and *Ficus religiosa* are considered holy trees by Hindus and Buddhists correspondingly, all around the globe. *Ficus religiosa* is considered the 'Bodhi tree' in which Gautama perceived light and meditated, thus arising as the 'enlightened one', Buddha. In accordance with the mythology of the Hindu religion, Brahma was changed into *Ficus benghalensis* (male), which is observed as the partner of *Ficus religiosa* (female) (Wilson & Wilson, 2013). In several treatises of Hinduism, an individual who plants both *Ficus benghalensis* and *Ficus religiosa*

protects themself from being transferred to hell (Jain & Kapoor, 2007). Since these species are believed to be the residences of gods, they are related to several taboos and beliefs. The Mikhir in the region of Assam assume that damaging or cutting *Ficus benghalensis* or *Ficus religiosa* is as sinful and immoral as murdering a saint (Jain & Kapoor, 2007), while all species of *Ficus carica* are regarded as sacred by all castes of the Hindu religion and never chopped down (Gadgil, 1987). In Asia, the Karbi people (in northeastern India) consider figs to be the sign of devils and demons. They particularly avoid giant groves of *Ficus benghalensis*, where ghosts or spirits are thought to live (Teron, 2009).

Figs are extensively esteemed for their sacred and spiritual properties and as a centre of attention for settling conflict. These plant species are never chopped down in Tanzania (Hines & Eckman, 1993), while in Rwanda and Burundi, ficus were significant in the worship of ancestral spirits and were sowed on the sites of the burials of previous kings (Wilson & Wilson, 2013).

People put flowers or grass at the foundation of *Ficus sycomorus* as an offering and, in response, ask their lord to reward them with blessings and provide them good luck in the region of Arusha. A similar species is worshipped by the capital city of Tanzania (Dodoma) as a water provider; moreover, in the countryside of Moshi, every leader must have the *Ficus thonningii* shade to sit, think and pray under (Hines & Eckman, 1993).

In some other places in the world, the *Ficus carica* or *Ficus sycomorus* is the first fruit tree mentioned in the Torah and the Bible: 'when the eyes of both Eve and Adam were opened, and they recognised that they were without clothes; they used leaves of fig as aprons' (Genesis 3:7). In traditions of Jews, King Solomon contrasted the Torah to the fig tree (Ginzburg et al., 1998) since 'just as precisely as an individual persistently discovers mature figs on a fig tree, so too will an individual every time perceive a new taste in the Torah when he is reading' (Guggenheimer, 2012). The fig tree is also among the seven species that their lord mentioned to the people of Israel regarding being in the pledged land of Israel (Craigie, 2007), and has been contemplated by some as a mark of the state of Israel. Moreover, there is also an Egyptian prehistoric belief that the plant *Ficus sycomorus* came out from Osiris' dead body (Budge, 1973).

The holy Quran also mentioned figs: 'By the fig and the Olea europaea!' (al-Hilālī et al., 2007). Hazrat Abu Darda describes that the Prophet Muhammad (peace is upon him) stated, 'consume fig, for it manages the piles and is beneficial for rheumatism'. Hazrat Abu Darda also narrates that somebody gave the prophet a fig plate, and he asked, 'Consume figs! If I stated a particular kind of fruit was bestowed to us from the paradise I would state its a fig since it is seedless' (Abbas, 2020).

Nutritional and Phytochemical Importance of Fig

Ficus carica is extensively produced for its fruit. Globally more than one million tonnes of fruits of *Ficus carica* are cultivated every year, with Turkey and Egypt growing almost half of the global supply. As a source of food, figs are chosen as a gift from God in the holy book of the Bible (Wilson & Wilson, 2013). The fruit of *Ficus carica* is often accessible in huge quantities and is extremely nutritious. They are a suitable source of nutrients, minerals, vitamins and fibre; (Vinson, 1999; Vinson et al., 2005). *Ficus carica* is among the best sources of fibre and calcium; in

accordance with the data from the United States Department of Agriculture, dried figs are enriched with calcium, potassium, magnesium, fibre, copper, manganese and vitamin K, relative to the requirements of humans. On the basis of weight, figs consist of more calcium (around 132.5 milligrams per 100 grams) than strawberries (14.01 milligrams per 100 grams), dates (25.0 milligrams per 100 grams), bananas (3.88 milligrams per 100 grams), raisins (40.0 milligrams per 100 grams), prunes (18.0 milligrams per 100 grams), apples (7.14 milligrams per 100 grams), oranges (40.25 milligrams per 100 grams) and grapes (10.86 milligrams per 100 grams). Recent research has demonstrated that the inclusion of fibre supplements in food material could assist in the loss of weight. Hence, *Ficus carica* and its fibre components may be beneficial in reducing weight since figs give more fibre, i.e. 12.21 grams per 100 grams, than all the aforementioned typical fruits (Vinson, 1999).

Studies about plant chemicals in *Ficus carica* showed the existence of several bioactive constituents such as organic acids, anthocyanin, phytosterols, triterpenoids, volatile constituents (i.e. aliphatic alcohols and hydrocarbons) and phenolic compounds; furthermore, many other groups of secondary metabolites from various other plant parts of figs (Gibernau et al., 1997; Oliveira et al., 2009).

Phenolics are a considerable component of fig fruit due to their impact on the fruit's colour, taste and nutritional values. Among the phenolics studied in the fig fruit, rutin is established in the greatest quantity around 28.7 mg per 100 grams (Veberic et al., 2008); after that 4.03 mg per 100 grams of catechin, 1.71 mg per 100 grams of chlorogenic acid, 0.97 mg per 100 grams of epicatechin, 0.38 mg/100 grams of gallic acid and ultimately 0.10 mg per 100 grams of syringic acid (Badgujar et al., 2014).

The *Ficus carica* leaves comprise several volatile constituents which are known and distributed by individual classes of chemicals, like ketones (3-pentanone), aldehydes (hexanal, 2-methylbutanal, [E]-2-hexanal, methylbutanal and [E]-2-pentanal), monoterpenes (menthol and limonene), psoralen, alcohols (phenyl ethyl alcohol, 1-penten-3-ol, benzyl alcohol, 2-methyl butanol, [E]-2-nonen-1-ol, heptanol, 3-methyl-1-butanol), sesquiterpenes (aromadendrene, germacrene D, τ -muurolene, α -muurolene, α -cubenene, α -ylangene, β -elemene, τ -cadinene, β -bourbonene, α -cubenene,copaene,α -gurjunene,α -caryophyllene,α -guaieneandβ -caryophyllene), norisoprenoids (β -cyclocitral), esters (methyl salicylate, methyl hexanoate, ethyl benzoate, methyl butanoate and hexyl acetate) and miscellaneous constituents (Oliveira et al., 2010).

Ficus leaves' organic acid profiling consisted of some organic acids, i.e. fumaric, citric, quinic, oxalic, shikimic and malic acids (Oliveira et al., 2009). The profile of ficus' amino acids was determined by HPLC combined with HPLC/UV-vis. It showed the existence of 13 constituents consisting of five EAA (essential amino acids), i.e. histidine, phenylalanine, leucine, lysine and tryptophan, and eight non-essential amino acids, i.e. cysteine, ornithine, serine, asparagine, tyrosine, alanine, glycine and glutamine. Tyrosine, cysteine and tryptophan are established in greater quantities compared to the other amino acids (Oliveira et al., 2010).

Luteolin emerged to be the principal flavonoid in the ficus leaf , representing a somewhat greater content of flavonoids as compared to quercetin. Luteolin is thought to have the probability of playing a considerable role in health, as it is considered to show wide-ranging anti-inflammatory effects (Jang et al., 2008), along with immunomodulatory, antioxidant, antimicrobial and anticarcinogenic activities. Inflammation, hypertension, cancer and several other diseases have been managed by using food enriched with luteolin in the traditional medicinal system (Lin et al., 2008). Gas

chromatography/ion trap mass recognised around seven plant sterols from the ficus latex extract. They are analysed with the help of HPLC combined with HPLC-DAD (diode array detection). The quantities of α-amyrin, β-sitosterol, β-amyrin, lupeol acetate, lanosterol, lupeol and betulol were 76, 10,564, 1,197, 1,989, 2,634, 2,827 and 327 mg/kg of the latex of plant, correspondingly. Hence, β-sitosterol is the constituent found in maximum quantities while α-amyrin is the slighter one (Shiraishi, 1996).

Anticancer Activity of Fig

Ficus carica demonstrates antitumour activity by means of diminishing effects on the multiplication of different cell lines of cancer. A study was conducted to analyse the anticancer outcomes of fig latex in various concentrations. Outcomes revealed that a 5 mg/millilitre concentration had the most significant effect in reducing gastric cancer cells growth (Hashemi et al., 2011). Another research revealed that latex, along with its derivatives, has been demonstrated to inhibit spontaneous and transplanted tumour growth (Ullman, 1952; Ullman et al., 1952). Cytotoxicity of the latex, leaf and fruit extracts on the cell line of HeLa was analysed, and outcomes revealed that various extracts and latex could inhibit the growth of HeLa cells at a minimum concentration of 2 μg/millilitre in a dose-reliant way (Khodarahmi et al., 2011). A blend of 6-O-acyl-beta-D-glucosyl-beta-sitosterols was separated as an efficient cytotoxic factor from the latex of fig, and the outcome verified in vitro decreasing effects on multiplication of different cell lines of cancer (Rubnov et al., 2001). Antiproliferative activity of latex and the outcome of the *Ficus carica* latex-TMZ (temozolomide) combinations were evaluated in the cell lines, i.e. U-87MG, T98G and U-138MG glioblastoma multiforme. Research data of the outcomes demonstrated *Ficus carica* latex giving rise to the death of a cell in glioblastoma multiforme with several reactions to temozolomide, and this outcome has been enhanced synergistically in amalgamation with temozolomide (Tezcan et al., 2015). Another study evaluated the anticancer effects of *Ficus carica* latex against human cancer cells, and outcomes established that there was a considerable alteration in 10 mg/ml latex treatment on the cancer cell line of the oesophagus after almost three days, and it was the suitable concentration for the reduction of cancer cell growth (Hashemi & Abediankenari, 2013).

Hepatoprotective Activity

The leaf extract of *Ficus carica* prepared in petroleum ether was assessed for its hepatoprotective activity on rodents managed with oral rifampicin at 50 mg per kilogram, and considerable turnaround of functional, histological and biochemical modifications persuaded by rifampicin on rodents specified possible hepatoprotective effect (Gond & Khadabadi, 2008).

Antidiabetic and Antiobesity Activities

Diabetes and obesity are two interconnected disorders and a public health concern globally. Both disorders' prevalence has been enhanced enormously in the past few eras (Ng et al., 2014). The WHO demonstrated that there are around 300 million

cases of obesity, and more than one billion adult people are overweight (Mopuri et al., 2018; Nguyen & El-Serag, 2010). Diabetes has been identified as one of the closely related health concerns to obesity in previous decades. The most important basis for this association is the obesity-related insulin resistance in the cells and the impairment of mechanisms for insulin secretion (Kahn & Flier, 2000). Therapeutic plants belonging to the *Ficus* genus have been documented as healing agents for metabolic ailments, while *Ficus carica* has gained more attention contrasted with other fig species since its fruit is generally consumed as a food item. The alcoholic extracts of fig fruit, which consisted of flavonoids and polyphenols in great quantities, demonstrated considerably greater antioxidant activity in vitro. The strong antioxidant activity of the fig fruit's alcoholic extract might be partially responsible for its antiobesogenic and antidiabetic activities, which have been verified by reducing a number of associated enzymes. Considerable reduction of enzymes that digest carbohydrates like α-amylase and α-glucosidase proposes that plant chemicals found in the fruit of *Ficus carica* could be lead constituents for the management of type 2 diabetes.

Two of the enzymes, α-amylase and α-glucosidase, are included in the hydrolysis of disaccharides and polysaccharides into simple molecules of sugars. The reduction of these enzymes may slow down the digestion process of carbohydrates and glucose liberation into the bloodstream (Giustarini et al., 2009). In addition to the chemical constituents such as 5-hydroxymethylfurfural, hexadecanoic acid and transphytol established in the extract of fig fruit have been demonstrated to have antiobesity and antidiabetic activity in a number of preliminary studies (Mopuri et al., 2018). The leaf extract persuaded a considerable blood glucose–reducing effect in the intraperitoneal or oral administration in streptozotocin-induced diabetic rodents. Levels of insulin in plasma significantly modified the index of survival in rodents. Outcomes specified that the water-based extract of fig has evident blood glucose–reducing effects (Chai et al., 2011).

Antioxidant Activities

Free radicals are responsible for causing damage to all cellular constituents, including lipids, proteins and DNA, while the damage to the cells in the regular state of redox can give rise to toxic outcomes by means of the synthesis of peroxides (Lobo et al., 2010). There has been a rising interest in utilising strong antioxidants for therapeutic reasons, specifically for the metabolic disorders associated with oxidative stress (Giustarini et al., 2009). The greater antioxidant activity of the various bioactive constituents in the alcoholic extract of *Ficus carica* fruit also confirmed that it is a possible source of antioxidants with free radical scavenging properties. The malic acid, 5-hydroxymethyl furfural and 2,5-dihydroxy-6-methyl- 2,3-dihydro-4H-pyran-4-one are known constituents in figs and have been stated as strong antioxidants in a number of current and previous research studies (Li et al., 2015; Yoshikoshi et al., 1996).

Antipyretic Activity

Alcoholic extract of figs at doses of 300, 200 and 100 mg per kilogram demonstrated a considerable dose-dependent drop in regular temperature of the body. The outcome lasted almost five hours after consuming the drug, contrasted to standard paracetamol (an antipyretic agent) (Patil et al., 2010).

Antihelminthic Activity

According to the World Health Organization, only some of the drugs are frequently consumed by human beings to manage helminths. These drugs are recognised as antihelminths which play an essential role in the management of parasitic infections. The antihelminthic activity of alcoholic, water-based, ether, petroleum and chloroform extract of *Ficus carica* leaves was studied against *Pheritima posthuma* in contrast with mebendazole as a standard medicine (Patil et al., 2010). This kind of activity is also stated in other varieties of ficus, i.e., *Ficus racemosa* Linn and *Ficus benghalensis* Linn (Latha et al., 2008). One of the chemical constituent coumarins has been separated from the alcoholic extract of fig leaves by bioassay-guided isolation, and the segregated coumarin demonstrated the most potent nematicidal activity in opposition to the nematodes *Caenorhabditis elegans*, *Bursaphelenchus xylophilus* and *Panagrellus redivivus* within three days (Liu et al., 2011).

Anticonstipation Effect

Constipation is among the most typical complaints of the gastrointestinal tract all around the globe. One of the studies analysed the effects of *Ficus carica* paste on the management of loperamide-persuaded constipation in a rodent model. For this reason, animals were distributed into one control group with normal rats and four investigational groups (30, 6, 1 and 0 grams per kilogram). At that point, 2 milligrams per kilogram of loperamide two times a day was introduced intraperitoneally to instigate constipation in the four investigational groups. The paste of *Ficus carica* was introduced for up to one month to assess its laxative effects and if it is beneficial in constipation or not. In the course of being done, the water content, weight and FPC (faecal pellet count) were found to be raised in the groups that were managed with figs in contrast with the control group.

Moreover, a drop in body weight and a rise in length of intestinal transit were noticed in the groups managed with *Ficus carica*. The number of faecal pellets was decreased in the terminal part of colons of the fig-managed rodents, while the exercise and tension of the ileum were raised in the investigational group in contrast with the control group. Fig fruit was established to inhibit constipation when given to rodents (Lee et al., 2012).

Moreover, an experimental study on humans (Kim et al., 2010) demonstrated that supplementation of *Ficus carica* fruit improved the clinical indications in patients with functional constipation. This clinical trial (RCT) of around 20 patients (female) showed that supplementation with the fruit of *Ficus carica* enhanced the frequency of stools, decreased defecation time and ameliorated abdominal pain. Hence, *Ficus carica* supplementation may be a beneficial preventive and therapeutic strategy for persistent and long-standing constipation (Badgujar et al., 2014).

Conclusion

Fig is unquestionably an important and beneficial source of food; meanwhile, it also has spiritual values in different religions. Humans are consuming figs in multiple ways.

Fig consists of polyphenols that have free radical scavenging and antioxidant properties, which are possibly beneficial for the health of humans. Fig could be a

potent alternative medicinal approach for managing obesity, oxidative stress and type 2 diabetes mellitus. However, several studies on experimental animals and humans are required to validate the traditional claims and therapeutic effects of *Ficus carica*; particularly the human data supporting all the ethnopharmacological and traditional claims about fig are still scarce.

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Chapter 23

What Milk and Dairy Products Can Do for the Human Body

Milk

Milk has been identified as one of the most nutritious and wholesome food products (Park, 2009); it is a white-yellowish coloured fluid produced by the mammary glands and secreted by the mammilla of female mammals while humans consume it as an edible, particularly for the subsistence of their progeny. Milk is a considerable energy source that consists of lactose, fats, water and proteins as dominant nutrients with vitamins, enzymes, soluble gases and minerals as micronutrients (Mourad et al., 2014; Soliman, 2005). Every species of female mammals acts as a milk source; however, bovine milk holds the leading commercial value since 83% of milk is acquired from bovine animals, and in order to fulfil the rising demand for dairy items globally, it has enhanced from 522 million to 828 million tonnes from 1987 to 2017 (more than 30 years) (Gerosa et al., 2012).

Globally, numerous people fail to acquire a sufficient amount of calcium from their diets. The sufficiency of consuming calcium by means of diet differs geographically and actually reveals a lot about the consumption of milk. In Europe, calcium consumption is generally decreased (Elmadfa, 2009), determined against the WHO/FAO recommended dose of nutrient intake (RNI) in adults, i.e. 1,000 mg/d, while consumption of mean calcium per day in around 16 European regions was 508 to 1,047 mg in women and 687 to1,171 mg in men (Elmadfa, 2009). Certainly, dairy items represent a remarkable source of calcium through diet because of their excessive nutrients and calcium contents, accessibility, comparatively decreased cost and great rate of absorption, which makes the daily intake of dairy items convenient. They give more protein, zinc, calcium, phosphorus, potassium and magnesium per calorie in contrast with any other particular edible in the diet of adults (Caroli et al., 2011; Heaney, 2009). Several dietary recommendations recommend the intake of dairy products as around three servings per day, i.e. one part of the cheese, a glass

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of milk and one part of yoghurt, a quantity that gives most of the Dietary Reference Intake of calcium for the overall population. For instance, 250 milligrams of calcium may be acquired from 35 grams of hard cheese, 125 grams of yoghurt or a 200-millilitre glass of milk (Rozenberg et al., 2016).

It has been demonstrated that the intake of dairy items, even those consisting of milk fat, does not cause hyperlipidemia and that milk and yoghurt could even have cholesterol-reducing outcomes (Hepner et al., 1979; Mann, 1974; Richardson, 1978).

Normally 30 to 40% of the calcium in cheese and milk is assimilated in the gastrointestinal tract either by means of vitamin D reliant transport through the duodenum, simplified diffusion or under the impact of lactose in the terminal part of the small intestine by means of the paracellular method (Caroli et al., 2011).

Calcium from the source of dairy products is believed to be at least as efficacious for the health of bones as calcium supplements, and perhaps to a greater extent (Heaney, 2009). A statement of agreement from the Belgian Bone Club proposes that for the non-medicinal treatment of osteoporosis, particular nutrient supplements will constantly be insufficient, and priority should go to the consumption of wholesome supplements or wholesome food products, for instance, dairy items (Body et al., 2011). Supplementation with calcium should only be suggested to those who can't get an adequate amount of calcium from their dietary sources and the ones who are susceptible to developing osteoporosis and/or getting fractures (Kanis et al., 2013).

According to Karen Giles-Smith, the milk of a cow is loaded with proteins of high quality, among which 18% is whey protein while 82% is casein. They are enriched with peptides that aid in reducing BP among patients with hypertension. Whey protein also consists of leucine (an essential amino acid) that gives energy for enhancing the volume of muscles and building up during extensive workouts and exercise (Giles-Smith, 2013).

Cyanocobalamin (vitamin B12) is an indispensable vitamin that is essential for the health of humans as it impacts cell division. Its lack may cause neuropathy and anaemia. Matte et al. (2014) discussed the significance of milk as a dietary source of cyanocobalamin for humans. Milk consists of calcium in increased quantities which strengthens the teeth and bones. Decreased calcium consumption may lead to rickets in the initial stages of life (Heaney et al., 2000). The milk of grass-fed cows has an ample amount of ω-3 fatty acids which are considered a good fat for enhancing the health of the cardiovascular system and protecting from various conditions of the heart such as myocardial infarction or stroke (Haug et al., 2007).

A study conducted by Khan et al. (2019) stated that milk holds antioxidant properties since milk has an ample amount of sulfur consisting of amino acids (AA) such as zinc, cysteine, selenium, superoxide dismutase, carotenoids, vitamin A, catalase, phosphate, vitamin E and enzymes. Dairy products, for instance, cheese and yoghurt, have peptides and oligosaccharides that too have antioxidant properties, which can counteract and work as scavengers of free radicals. They aid in preventing the human body from injurious outcomes. These free radicals ultimately give rise to cardiovascular ailments, cancer and diabetes. Moreover, they enhance the process of ageing as they initiate oxidative stress, which disturbs biochemical combinations such as lipids, DNA and protein (Khan et al., 2019).

Goat milk consists of medium-chain triglycerides that aid in the absorption of nutrients and give energy to the body. Goat milk also contains bioactive constituents such as glycolipids, glycosphingolipids, gangliosides and cerebrosides. These

bioactive fats work as antibodies and aid in the detection of antigens and microbial toxins such as enterotoxins and cholera. An amino acid, taurine, is also found in goat milk and plays a significant role in the development of the brain and the growth and synthesis of bile salts. Its lack may lead to cardiomyopathy, growth retardation and epilepsy (Zenebe et al., 2014). Goat milk also consists of oligosaccharides and is useful in providing nutrition to the human body due to its anti-infective and prebiotic activities. The oligosaccharides of goat milk have been demonstrated to possess anti-inflammatory effects against instigated colitis in animal models (Lara-Villoslada et al., 2006). Conjugated linoleic acid, also found in goat milk, has anti-inflammatory and anti-allergic properties as it inhibits the synthesis of cytokines, immunoglobulins and prostaglandins that are related to IBS (irritable bowel syndrome), atherosclerosis and cancer (Park, 2009).

Cardiovascular disorder is one of the principal reasons for death globally (Rozenberg et al., 2016), while the impact of diet on identified risk factors such as body weight, serum cholesterol and blood pressure is well accepted. Accordingly, the dietary approaches to stop hypertension (DASH)-style diet, which includes moderate quantities of low-fat dairy products, has been advised to prevent stroke, coronary heart disease, cardiac failure and other cardiovascular ailments (Salehi-Abargouei et al., 2013).

Dairy Products and Their Health Benefits

Dairy food items have been a significant fraction of the human diet for around 8,000 years and are considered a part of the authorised dietary recommendations in numerous regions globally. They give a lot of essential nutrients that are arduous to acquire from diets with restricted or no dairy items, such as restrictive dairy diets or veganism. Undoubtedly, dairy food is enriched in calcium, potassium, phosphorus and protein. Dairy food provides nearly 52 to 65% of the DRI (Dietary Reference Intake) of calcium and 20 to 28% of the protein requirement, based on the consumer's age (Rozenberg et al., 2016). Around two-thirds of the calcium consumption among people living in western countries is provided by dairy food (Guéguen & Pointillart, 2000). Simultaneously dairy products constitute only 9 to 12% of the overall energy intake (Bonjour, 2011).

Fermented milk products are loaded with numerous minerals and vitamins, and they are particularly bioavailable. They demonstrate a significant contribution of calcium, magnesium, potassium iodide, phosphorus, vitamin D, zinc, potassium, niacin, folic acid, pantothenic acid, and vitamins A, B12, B6, B2 and B1. A number of these microconstituents have increased bioavailability in fermented dairy products compared to raw milk because of the fermentation and acidity, which predominantly affects the vitamin content (Frias et al., 2017; García-Burgos et al., 2020).

One of the studies describes that signs of fermented dairy products have been established as early as 8000 BC in eastern parts of Europe and Asia Minor, promptly after the domestication of milk-producing animals (sheep, cow and goats) (Ray & Montet, 2017). Proofs of kefir intake were established in the Bronze Age tombs of China (Yang et al., 2014). The initial dairy food items resembling yoghurt were devised in Mesopotamia about 5000 to 6000 BC. Historians think the Thracian tribe Bizalti were the pioneers of intentionally manufacturing fermented dairy foods (Petrova et al., 2021). One more instruction related to the exploration for the

commencement of lactic acid fermentation of dairy products is provided by the elucidation of Herodotus (Greek historian), in accordance with whom a group of old tribes of nomadic warriors (Scythians) used sour milk (Fisberg & Machado, 2015).

Over 45 billion (MT) metric tonnes of fresh dairy products are taken in Europe each year. The regions of the European Union produced 6.1 billion metric tonnes of yoghurt and 6.4 billion metric tonnes of cheese in 2019. In 2020, Bulgarian dairies processed 663,644,000 litres of unpasteurised milk, with cow's milk accounting for 94.3% (Petrova et al., 2021).

Yoghurt

Yoghurt is the traditional product that is developed by the fermentation of milk and is thought to have been discovered approximately 4,000 to 6,000 years ago; it is mentioned in a few Indian sacred books such as Upanishads and Vedas. The intake and manufacturing method of yoghurt has been documented in India since 2000 BC (Mallappa et al., 2021).

The therapeutic activities of Bulgarian yoghurt have been identified in Europe at least since 1542 when Francis I (king of France) was treated for persistent diarrhoea with a plain yoghurt diet (Ray & Montet, 2017). A Bulgarian medical school student, Stamen Grigorov, was the pioneer who reported about the rod-shaped *Bacillus bulgaricus grigorov*, accompanied by a *Streptococcus* species, in yoghurt (Stoilova, 2014). On the basis of Grigorov's outcomes, in 1909, winner of the Nobel Prize and the Russian life scientist Elie Metchnikoff evolved his theory regarding the extension of life; he was the first to advise that regular intake of yoghurt promoted the longevity of the peasant people of Bulgaria, particularly in the mountainous areas. Metchnikoff proposed that there is an association between the number of centenarians in Bulgaria and the intake of yoghurt. He further suggested the hypothesis that the reduction of injurious fermentation of food in the gastrointestinal tract can impede the ageing process. At the core of his study is lactic acid, which decreases the amount of putrefactive or septic microbes (Mackowiak, 2013; Stoilova, 2014).

Yoghurt has religious importance as a holy food product and is utilised in many spiritual festivals and ceremonies among Buddhists and Hindus. Traditional yoghurt is manufactured by cooling buffalo or cow milk to room temperature, subsequently adding artisanal cultures (acquired by the black slopping method) which are permitted to develop and multiply overnight or within two to four days gradually, depending on the season, till the adjusted product is established. Commercially, yoghurt is synthesised by fermentation of boiled or pasteurised cow or buffalo milk, utilising both moderate temperature (mesophilic) and heat-loving (thermophilic) determined starters in different blends. The frequently established LAB cultures in preparation of yoghurt are strains of *Lactococcus lactis* ssp. *cremoris*, *Streptococcus thermophilus*, *Lactobacillus acidophilus*, *Lactococcus lactis* ssp. *lactis*, *Lactobacillus helveticus*, *Lactococcus lactis* ssp. *lactis biovar diacetylactis* and *Lactobacillus delbrueckii* ssp. *bulgaricus* (Mallappa et al., 2021). Moreover, many authors have investigated the microbial variation of yoghurt utilising culture-reliant methods (Koirala et al., 2014; Soomro & Masud, 2007) (Table 23.1).

Modifications in milk caused by fermentation during the preparation of yoghurt can be abridged as the synthesis of acids, the fermentation of 20–30% of milk lactose to LA (lactic acid), enhancement in digestibility of milk, the changes in

Table 23.1 Microbial Variations Found in Naturally Fermented Yoghurt

Name of microbe	*Quantity*	*Reference*
Streptococcus	50%	(Koirala et al., 2014)
Lactobacillus	27%	
Enterococcus	9%	
Leuconostoc	5%	
Lactococcus	5%	
Pediococcus	4%	

the content of vitamins and escalated quantities of free amino acids (Desobry-Banon et al., 1999).

Yoghurt is also consumed as a preventive agent in Ayurveda for several diseases such as vomiting, dysentery and bleeding ailments due to its multifunctional properties (Priyanka & Jayavarma, 2014), such as being a blood purifier; yoghurt was established to be beneficial in managing associated blood disorders, gastrointestinal ailments and piles. Apart from nutritional characteristics, yoghurt is also believed to enhance the health of the gastrointestinal tract by efficient colonisation of beneficiary microbes heading towards normalisation of dysbacteriosis persuaded by several factors, such as stress, food contamination, variation in regular diet and deficiency of prebiotic constituents. This can be associated with the demonstration of antibacterial activity of yoghurt against several infectious agents such as *Salmonella typhi*, *Staphylococcus aureus*, *Bacillus cereus*, *Shigella dysenteriae*, *Escherichia coli*, *Enterobacter agglomerans*, *Micrococcus flavus*, *Enterobacter aerogenes*, *Klebsiella pneumonia* and *Enterobacter cloacae* (Dewan & Tamang, 2006; Samanta et al., 2015). Yoghurt synthesised by goats was discovered to invigorate the mucosal immune system and made the defensive system better against pulmonary and enteric infections in an immune repression model in mice (Babaee et al., 2011; Morita et al., 2006). The accessibility of antidiabetic factors in the yoghurt of camel milk further expanded the biomedicinal potential of yoghurt in diabetes-associated disorders (Fallah et al., 2018).

The health benefits of yoghurt include the prevention of cancer and enteric inflammations, as the impact of lactic acid–producing bacteria (LAB) and yoghurt on inflammation of intestines and cancer have been researched extensively. The protective outcome of probiotics on cancer development may be related to the regulation of the immune reaction and modifications in the enteric microbiota, protecting the rise in a microbe that set off as pre-carcinogens to carcinogens. (de Moreno de Leblanc & Perdigón, 2010). In a colon carcinoma model of rodents, the intake of yoghurt reduces the growth of the tumour by decreasing inflammatory reaction through apoptosis, the upsurge of interleukin-10 releasing cells, and the reduction of the enzymes pro-carcinogenicas (de Moreno de Leblanc & Perdigón, 2010).

Kefir

The origination of kefir from the Caucasus, Mongolian or Tibetan mountains, was prior to 2000 BC; the kefir grains were traditionally handed over from one generation

to another generation amid the tribes of the Caucasus, being thought of as a family's wealth source (Rosa et al., 2017). Kefir is one of the dairy products which varies from other fermented foods since it is synthesised by grains that consist of a particular compound blends of acetic acid and lactic acid–producing microbes; moreover, lactose non-fermenting and fermenting yeast, which survives in a symbiotic relationship (Lopitz-Otsoa et al., 2006). The microbes found in kefir have the potential of probiotics. Many microbe species separated from kefir revealed high resistance to bile salts and low pH in the gut and are capable of attaching to the mucosal surface of the intestine (Golowczyc et al., 2008). Kefir has enhanced curiosity among the researchers because of its proposed useful activities including lactose tolerance, enhanced digestion capability, antimicrobial, blood glucose regulating, antihypertensive, hypocholesterolemic, antioxidant, anti-allergenic, anti-inflammatory and anticarcinogenic activities (Rosa et al., 2017).

Furthermore, minerals, for instance, Fe, Cu, Mo, Zn, Co and Mn, are present in milk kefir. The amount of evidence signifies that probiotic microorganisms or their products play a significant role in regulating BP. Antihypertensive activity has been noticed in clinical and experimental research studies (Rosa et al., 2017); however, the data is controversial and restricted. Quiros et al. established that kefir can decrease the ACE (angiotensin-converting enzyme) activity by activating the bioactive peptides produced from casein throughout the process of milk fermentation (Quirós et al., 2005). Maeda et al. observed the antihypertensive activity because of the kefiran's ability to reduce the angiotensin-converting enzyme activity (Maeda et al., 2004).

Kefir demonstrates many positive health outcomes including anti-allergenic, wound healing, antibacterial, immunomodulation, cholesterol metabolising, anticarcinogenic and gastrointestinal health-maintaining effects (Bourrie et al., 2016). Kefir synthesises a high level of interferon-γ and tumour necrosis factor-α that can give rise to enhanced secretions of immunoglobulin-A (Sharifi et al., 2017). On the contrary, kefir has been demonstrated to have a multitude of antifungal and antimicrobial activities. It has been established that kefir has an identical function to azithromycin, amoxicillin, ceftriaxone, ampicillin and cetoconazol (García-Burgos et al., 2020).

Fermented Milk

The useful properties of fermented milk items for the health of humans have been researched extensively since the assertion of Metchnikoff et al. (1907) that fermented dairy products encouraged the extension of life by endeavouring a positive impact on the flora of the gastrointestinal tract (Bakalinsky et al., 1996).

Cheese

Cheese is described as an edible in which the proportion between casein and whey protein is not greater than milk. It comprises harmless microbial culture ferments synthesising lactic acid and/or modifiers of aroma and taste, cultures of other least harmful or safe microbes and appropriate harmless enzymes. The intake of cheese has been demonstrated to be useful in muscle building, inhibition of LDL cholesterol

and blood pressure and prevention of obesity, diabetes, tooth decay and cancer (García-Burgos et al., 2020).

Clarified Butter/Cow Ghee

Clarified butter has been extensively used in Ayurveda for millennia because of its health-enhancing properties. It is either given alone or combined with herbs to manage several ailments. There are around 55 to 60 varieties of therapeutic ghee reported in the ancient texts of Ayurveda (Tamime, 2009). Positive outcomes have been discussed in a research study conducted on various blends of ghee. As discussed, medicated clarified butter showed blood cholesterol-reducing effects in patients with psoriasis and considerably ameliorated psoriasis-associated symptoms (Sharma et al., 2010). The herbal blend Maharishi Amrit Kalash-4 decreases the low-density lipoprotein oxidation in patients with hyperlipidemia (Hanna et al., 1996; Sundaram et al., 1997). Combinations consisting of clarified butter (ghee) have also demonstrated hepatoprotective outcomes (Achliya et al., 2004a), intensifications in the healing of the wound, increase in memory (Prasad & Dorle, 2006) and anti-convulsing activities (Achliya et al., 2004b).

Ghee or anhydrous milk fat is manufactured by heating cream or butter to just more than 100° C to eliminate the water content by boiling, vaporising and subsequently sieving out the precipitated solid particles of milk. Clarified butter is also recognised as *ghrita* in Ayurveda (Sharma et al., 2010), which is a nutritious source of consumable fat with numerous useful properties. In accordance with Ayurveda, clarified butter encourages longevity and protects the body from different ailments (Tirtha, 2007). It enhances the *agni* (digestive fire) and improves absorption and digestion. It provides nourishment to the *ojas* (one of the essences of vitality). Clarified butter is also stated to provide strength to the nervous system, enhance memory and provide lubrication to the connective tissues, thus providing more flexibility to the body. With respect to the three bodily humours (*doshas*), clarified butter pacifies *pitta* and *vata dosha* and is bearable for *kapha* in moderation (Lad, 1999).

In Ayurveda, clarified butter is extensively used for many therapeutic applications; its uses include the management of dermatological ailments, allergies and pulmonary disorders. Numerous preparations of Ayurveda are produced by combining herbs with ghee (clarified butter), and ghee acts as a carrier to provide the medicinal properties of herbs to the overall tissues of the body. It is a remarkable vehicle (*anupana*) for taking herbs to the inner layers of the body tissues (Lad, 1999). Complete assimilation, absorption and transportation to an intended organ system are pivotal in achieving the greatest benefit from any medicinal composition; the lipid-loving (lipophilic) property of ghee (clarified butter) encourages delivery to an intended organ and ultimately delivery to the interior of the cell because the cell membrane also consists of lipids (Sharma et al., 2010). One of the research that contrasted various forms of herbal extracts and herbs established that the efficacy of herbs was enhanced when they were consumed with clarified butter (ghee), in contrast with their consumption in tablet or powder form (Illingworth et al., 2009).

Clarified butter enhances intellect and intelligence and acts as a lubricating agent over the gastrointestinal tract walls, and facilitates effortless expulsion of undigested food particles. Ghee can be utilised as a moisturiser and bath oil;

moreover, it is also beneficial for healing wounds. In recent times several studies have confirmed that ghee is beneficial for health (Kumar et al., 1999).

There are lots of clarified butter or ghee-based compositions that are suggested for preservation and encouragement of neurological health, which include *Brahmi ghrita*, *Kalyanaka ghrita*, *lashunadi ghrita*, *mahakalyan ghrita* and *mahapaishachika ghrita* (Sharma & Chandola, 2015).

Composition of Clarified Butter

Clarified butter has been utilised for culinary, religious and therapeutic reasons since the Vedic period. The significance of clarified butter in Indian diets has been identified from the primaeval era due to its enormous dietary values, textural characteristics and gratifying aroma. It is prepared with cream, butter or milk from various animals. Clarified butter is considered a food filled with energy and loaded with EFAs (arachidonic acid and linolenic acid), growth-enhancing factors and fat-soluble vitamins (Sindhuja et al., 2020). Predominantly, clarified butter is comprised of omega fatty acids, saturated fat, fatty acids, cholesterols, trans fat, vitamin A, vitamin D, vitamin B, polyunsaturated fats, vitamin K, monounsaturated fat, vitamin E and a small quantity of water. Ghee consists of fat-soluble vitamins and EFAs, which cannot be prepared in the human body (Sindhuja et al., 2020). The fat constituents of milk such as butyric acid, sphingomyelin, conjugated linoleic acid and other lipids possessing anticancer capabilities are also provided by clarified butter (ghee) (Akalin & Tokusoglu, 2003). It consists of an antioxidant such as beta carotene and vitamin E apart from other nutrients such as diglycerides, phospholipids and triglycerides. Clarified butter prepared from cow milk is identified to be digested by almost 96%, which is splendid as contrasted with various animal or vegetable supplies of fats (Sindhuja et al., 2020). With respect to the nutritional aspect, clarified butter is more dependable than other fats/oils because of its content of medium-chain FAs, which are directly absorbed by the liver and burned to provide energy (Kumar et al., 2018). It is reasonably shelf-stable because of natural antioxidants and minimum moisture contents. Casein- or lactose-intolerant individuals have found no issues with the consumption of ghee due to the elimination of impurities and solid particles of milk (Sindhuja et al., 2020). Because of the characteristic of short-chain FAs content, clarified butter has been universally accepted as the best fat, responsible for its better absorption and anticancer properties (A. Kumar et al., 2018).

The study of fatty acids in residues of clarified butter demonstrated that the palmitic acid recorded the highest (38.88) among SFAs. In contrast, oleic acid was reported in the highest quantity (25.15) of unsaturated fatty acids. The docosahexaenoic acid, linolenic, eicosapentaenoic and linoleic acid content of clarified butter residues were 0.25, 0.79, 0.36 and 2.02%, respectively, while the study of amino acids showed that the content of methionine and lysine were 0.61 and 0.99%, correspondingly. Arginine and threonine levels are noted to be at 0.76 and 1.44%, respectively. The glutamic acid was documented in the utter best quantity (5.26), while cysteine was recorded in the minimum proportion amid other amino acid residues in clarified butter. Hence, clarified butter residues are a rich source of protein, fats and unsaturated fatty acids (Ramesh et al., 2018) (Table 23.2).

Table 23.2 Medicated Ghee (Clarified Butter) and Its Medicinal Uses

Medicated ghee	*Composition of herbs or minerals used in combination with ghee*	*Proven health benefits*	*References*
Ashwagandha ghee/*ghrita*	Milk, the root of *Withania somnifera*, water and clarified butter	*Ashwagandha* is extensively claimed to have immunomodulatory, antidepressant, cardio-protective, antitumour, antimicrobial, antioxidant, anxiolytic, anti-inflammatory, antistress, nootropic, anticonvulsant, antigenotoxic, hepatoprotective, antiparkinsonian activities. *Ashwagandha* ghee is also an efficient formulation useful for the management of general weakness, gynaecological disorders and infertility	(Kumar et al., 2015; Pérez-Gómez et al., 2020; Pratte et al., 2014)
Jatikalpa ghrita	*Myristica fragrans*, *Curcuma longa*, *Pongamia pinnata*, *Woodfordia fructicosa*, *Rubia cordifolia*, *Symplocos racemosa*, *Glycyrrhiza glabra*, *Azadirachta indica*, *Hemidesmus indicus*	Antioxidant, anti-inflammatory, and wound healing	(Sathish et al., 2018; Sindhuja et al., 2020)
MAK-4 (Maharishi Amrit Kalash-4)	Clarified butter, cinnamon, *Curcuma*, *Cyperus scariosus*, sugar, *Piper longum*, *Terminalia chebula*, *Bacopa monnieri*, *Cyperus rotundus*, *Emblica officinalis*, *Mesua ferrea*, *Embellia ribes*, honey, *Convolvulus pluricaulis*, *Santalum album* and liquorice	MAK-4 has immunomodulatory, anticarcinogenic, antioxidant activities, and it considerably improved prompted splenic synthesis of interleukin-2, prevent 7,12-dimethylbenz(a)anthracene-induced carcinoma of the mammary gland and aggressive lung carcinoma in rodents	(Inaba et al., 1995; Penza et al., 2007)

(*Continued*)

Table 23.2 (Continued) Medicated Ghee (Clarified Butter) and Its Medicinal Uses

Medicated ghee	*Composition of herbs or minerals used in combination with ghee*	*Proven health benefits*	*References*
Mahatiktaka ghrita	Triphala, *Tinospora cordifolia, Alstonia scholars, Picrorrhiza kurroa, Citrullus colocynthis, Adhatoda vasica, Asparagus racemosus, Cassia fistula, Vetiveria zizanoids, Cyperus rotundus, Azadirachta indica, Cissampelos pariera, Santalum alba, Holarrhena antidysenterica, Gentiana kurroo, Glycyrrhiza glabra, Prunus cerasoides, Swertia chiraita, Curcuma longa, Acorus calamus, Piper chaba, Trichosanthes dioica, Fumaria indica, Hemidsemus indicus, Berberis aristata, Marsdenia tinescsima, Alhagi pseudalhagi, Piper longum, Aconitum heterophyllum*, juice of *Emblica officinalis* and clarified butter	This medicated ghee is quite beneficial in relieving anaemia, bleeding, piles, erysipelas, eruptions, menorrhagia, internal bleeding, gouty arthritis, itching, eczema, jaundice, boils, abdominal tumours, leprosy, inflammation and another chronic stubborn disease	(Caraka, 1996)
Brahmi ghrita	Juice of *Centella asiatica*, clarified butter, 30 grams each of *Convolvulus arvensis, Saussurea lappa* and *Acorus calamus*	It acts as a nervine tonic and is quite beneficial for scholars and students for forgetfulness, physical and mental fatigue	(Puri, 2003)
Bhallatakadi ghrita	Eighty grams of *Semecarpus anacardium*, 40 grams of *Vidarigandhadi pancamula* (grounded powder of five roots), i.e. *Desmodium gangeticum, Solanum indicum, Uraria picta, Tribulus terrestris* and *Solanum xanthocarpum*, along with 2.56 litres of water, 640 grams of clarified butter and 640 ml of milk	*Bhallatakadi ghrita* has wound healing properties and is an outstanding remedy for *kaphagulma* (abdominal tumour of *kapha* origin). It also helps in managing anaemia, spleen enlargement, asthma and cough	(Caraka, 1996; Wayal & Gurav, 2020)
Arjuna ghrita	Clarified butter, *Terminalia arjuna*	It has anti-inflammatory, antioxidant and cardio-protective effects; moreover, it inhibits the levels of cholesterol in the blood and hence is beneficial in cardiovascular diseases	(Dwivedi, 2007; Gandhi & Lal, 2015)

(*Continued*)

Table 23.2 (Continued) Medicated Ghee (Clarified Butter) and Its Medicinal Uses

Medicated ghee	*Composition of herbs or minerals used in combination with ghee*	*Proven health benefits*	*References*
Saraswat ghrita	25 grams each of calamus, salt, *Embellia ribes* and sugar, 750 grams of clarified butter, 50 grams each of *Terminalia chebula*, *Curcuma longa*, *Ipomoea turpethum*, *Saussurea lappa*, jasmine flower and juice of *Centella*	This composition enhances intelligence and virility; hence it is suggested to use for enhancement of memory and sexual power. Furthermore, it is also considered beneficial in all kinds of dermatological disorders	(Puri, 2003)
Shatavari ghrita	Juice of *Asparagus racmosus*, clarified butter, milk, *Pterocarpus santalinus*, *Pueraria tuberosa*, black grapes, *Glycyrrhiza*, *Uraria picta* and *ashtavarga* (a group of eight herbs in Ayurveda)	*Shatavari ghrita* is a diuretic and antispasmodic agent which aids in providing strength to patients for overcoming the effects of chemotherapy during the management of cancer. It also boosts immunity and has several other identified health-enhancing properties for females. Moreover, it has antidiarrheal, antioxidant, hepatotoxic and antioxytocic activities	(Goyal et al., 2003; Puri, 2003)

Dairy Products in Boosting Immunity

One of the studies (Perdigon et al., 1995) reviewed the outcomes of feeding yoghurt and LAB on the systemic immune reaction in rodents and deduced that yoghurt could minimise intestinal cancer growth by means of the escalated activity of immunoglobulin-A secreting B cell macrophages and T lymphocytes. The provocation of the immune system in humans has also been noticed. In 1991, Halpern et al. documented an increase in the synthesis of lymphocyte's γ-interferon in humans of young age subsequent to a diet with two cups of yoghurt a day for four months (Halpern et al., 1991). The elicitation of cytokines in humans by microbes utilised in dairy products was researched in vivo and in vitro by Solis Pereyra and Lemonnier (1993). While in 1994, Losacco et al. estimated the impact of taking yoghurt on enteric immunity among cancer patients subsequent to colorectal resection. Ten of the patients, varying between 44 and 85 years of age, going through surgery from 1989 to 1992, were suggested a regular quantity of 500 g yoghurt (skimmed) for around four weeks. Yoghurt stimulated an excessive release of gamma-interferon with CD4+and CD8+cells activation (Losacco et al., 1994). Aattouri and Lemonnier (1997) demonstrated the activity of *Streptococcus thermophilus* more accurately in inducing the synthesis of interferon (Aattouri & Lemonnier, 1997). Reddy et al. were the first to document an anticarcinogenic activity of yoghurt in rodents, and thenceforth, research studies on exploratory cancers persuaded in animals showed that strains of yoghurt are capable of decelerating tumour development (Perdigon et al., 1995; Reddy et al., 1983).

Kefir exerts microbial killing activities on gram-negative microorganisms, though it is more powerful against gram-positive microorganisms (Rosa et al., 2017). This antagonistic activity has been noticed against *Staphylococcus*, *Salmonella* and *Shigella* bacteria (Rodrigues et al., 2005; Rosa et al., 2017), *Micrococcus luteus*, *Proteus vulgaris*, *Escherichia coli*, *Bacillus subtilis*, *Enterobacter aerogenes* (Kwon et al., 2003), *Helicobacter pylori* (Oh et al., 2002), *Streptococcus pyogenes*, *Listeria monocytogenes* and also in opposition to *Candida albicans* (Rodrigues et al., 2005). One of the studies reported kefir activity against *Shigella sonnei*, *Candida albicans*, *Salmonella typhi*, *Staphylococcus aureus* and *Escherichia coli* (Silva et al., 2009). Ulusoy et al. noticed that kefir-synthesised commercial lyophilised grain (Probate KC3; Danisco) demonstrated antimicrobial activity against *Salmonella enteritidis*, *Escherichia coli*, *Staphylococcus aureus*, *Listeria monocytogenes* and *Bacillus cereus*. The outcomes were analogous to gentamycin and ampicillin (Ulusoy et al., 2007).

The SARS-CoV-2 that is inflicting devastation around the globe gets entrance to cells by adhering to the angiotensin-converting enzyme-2 that functions as a coronavirus receptor. It is proposed that the inhibitory peptides of angiotensin-converting enzymes can assist in concealing the sites of attachment for coronavirus and can therefore prevent its binding to the cells. Thus, intake of fermented products can possibly bring about the prevention from the infection of coronavirus (ARIA Group et al., 2020).

Dahi (yoghurt) is a fermented milk product that consists of probiotics that function as an immunostimulator and prevent inflammatory disorders such as IBD (inflammatory bowel disease) (Lorea Baroja et al., 2007). Yoghurt is used in patients with human immunodeficiency virus and hepatitis and is also found to be useful in patients with lactose intolerance (Akram et al., 2020).

Conclusions

Milk and its products are suggested as healthy edibles throughout all periods of life, particularly during adolescence and childhood, as their contents of phosphorus, calcium, protein and other micronutrients might encourage the development of neurologic, muscular and skeletal systems. The chapter discussed milk and some of its derivatives as functional foods. Generally, dairy items give a firm and stable base of nutrition for weight loss. The functional constituents of dairy products substantially contribute to the prevention of diseases such as diabetes, obesity, hypertension, cancer and many transmissible disorders. There are many types of applications of dairy compounds, such as nutritional supplements, pharmaceutical products, and the cosmaceutical industry. The chapter has also shed some light on the benefits of various medicated clarified butter (ghee/*ghrita*). Ghee is considered superior to other forms of fats because it consists of fat-soluble vitamins, short-chain fatty acids and essential fatty acids. Clarified butter or ghee has been frequently consumed in Ayurveda for various medical conditions.

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Chapter 24

Triphala

A Compound Detoxifying Herbal Preparation

Introduction

Triphala, the 'tridoshic Rasayana', is the most prominent Ayurvedic medicine. Here, the word tridoshic describes maintaining or keeping all three *doshas* (*vata*, *pitta*, *kapha*) in a balanced state and detoxifying the body. This composition is the combination of three myrobalans, i.e. *Emblica officinalis* (*amla*), *Terminalia chebula* (*halila*) and *Terminalia bellirica* (*bahira*); all three of them are in equal proportions (Figure 24.1). A changed formulation of 1:2:4 parts of chebulic myrobalan, beleric myrobalan and emblic myrobalan, respectively, is also consumed (Nariya et al., 2009). Triphala consists of a diverse range of plant chemicals (Figure 24.2) that exert rejuvenating and reinvigorating effects on the human body and raise life expectancy in patients of all ages and *doshas* (Baliga, 2010).

The old Sanskrit medical pieces of literature named *Caraka Samhita* and *Sushruta Samhita* also mentioned triphala multiple times. According to *Caraka Samhita*,

> One fruit of Terminalia chebula after assimilation, two fruits of Terminalia bellirica after a meal and four fruits of Emblica officinalis after a meal should be consumed with honey and clarified butter for a year, it can prolong the life of a person for 100 years without any disease or old age.
>
> (Caraka et al., 2001)

Whereas the *Sushruta Samhita* states that the formulation of triphala is beneficial for managing wounds and ulcers (Bhishagratna, 2014). Triphala has been used to

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Figure 24.1 Triphala.

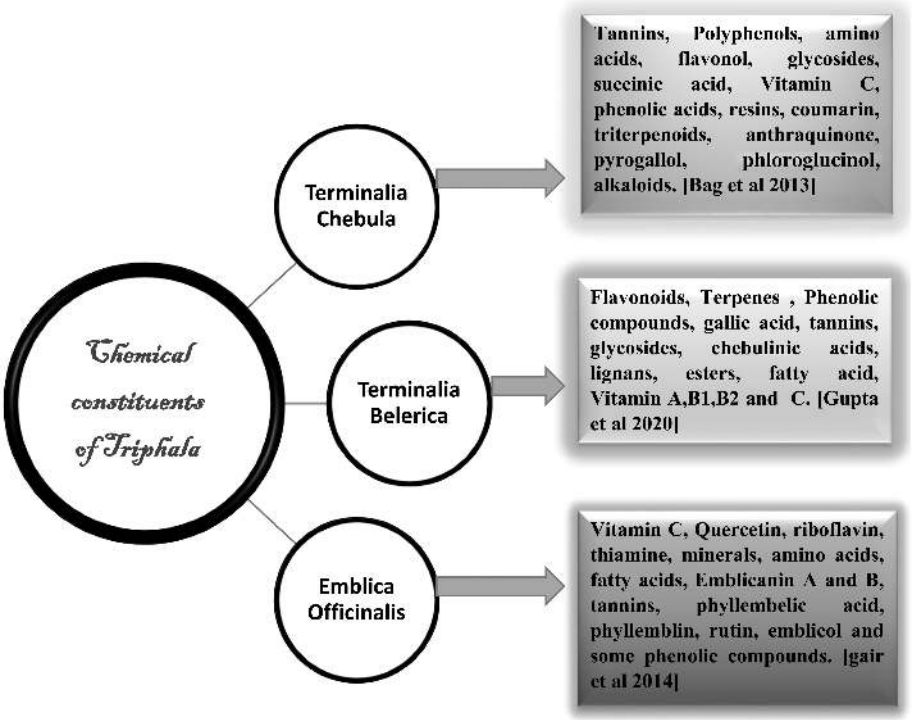

Figure 24.2 Phytochemical constituents of triphala.

manage gastrointestinal disorders, such as nausea, vomiting, indigestion, constipation, non-bleeding piles and colon cleansing, and is also advised in CVD, diabetes mellitus, hepatic dysfunction, chronic inflammatory conditions, ophthalmic conditions, cough, leucorrhea, ulcers, pyorrhea/scurvy, fever, hypertension, inflammatory bowel disease and hypercholesterolemia (Nadkarni & Nadkarni, 1998). As we know, both eastern and western medicinal systems reach a consensus that health and sickness initiate from the gastrointestinal tract, and triphala is excellent preparation for maintaining the gut's health. Triphala facilitates assimilation, absorption, excretion and reinvigoration (Caraka et al., 2001; Hippocrates et al., 1978). Historically, it was considered that triphala in its powdered form consumed with clarified butter regularly turned out to be a panacea or solution for all diseases because it was empowered with revitalising features (Bhishagratna, 2014). The number of references in highly regarded Ayurvedic medical literature elucidates that triphala is admired as a versatile healing remedy because of the presence of highly beneficial medicinal fruits in its composition, all collectively identified by astringent taste with a blend of a sweet and bitter taste. According to Dr Vasant Lad, triphala is *pancha rasa alavana* which means it has five tastes apart from the salty taste. There are rare situations where the taste of triphala feels sweet, i.e. when there are no toxins in the body, and all seven body tissues or *dhatus* are balanced flawlessly; at that time, consumption of triphala should be discontinued (Lad, 2002).

History of Triphala

The foundation of Ayurveda is based upon a few basic concepts, which include that the human body is composed of seven kinds of *dhatus* or body tissues (i.e. *rasa*/plasma, *rakta*/blood, *mamsa*/muscle, *meda*/fat, *asthi*/bone, *majja*/bone marrow and *sukhra*/reproductive fluids), *tridoshas* (*vata*, *pitta*, *kapha*) and *trimala* (waste products of the body, i.e. urine, stool and sweat); all of them are created by five physical elements or *pancha maha bhootas*: air, fire, ether, earth and water. Among all three *doshas*, *pitta* (*agni*/fire/bile) is associated with gastric enzymes and juices accountable for bioconversion and assimilation of medicines, food and other constituents (Caraka, 1996; Rao, 2004); moreover, *pitta* is believed to generate and preserve the heat in the body while *vata* (air) tends to be linked with the movement of the body and nervous system. Though *kapha* (water) depicts moistness or hydration of sensory organs and tissues of the body, *vata* promotes catabolism, whereas *pitta* and *kapha* encourage anabolism. This concept of five essential elements and *tridoshas* resembles the concept of elements, humours and temperaments in Greco-Arabic medicine (Puri, 2003; Rao, 2004), as in Greco-Arabic medicine, there are four basic elements, i.e. air, water, fire and earth, which makes four essential humours, i.e. blood, yellow bile, phlegm and black bile. The traditional pieces of literature, including *Sushruta Samhita* and *Charaka Samhita*, were inscribed hundreds of years ago to give detailed information about the diagnosis and management of diseases, how to prepare certain medicines and which medicines affect which humour and organ of the body (Baliga et al., 2012; Caraka, 1996); these ancient literature discusses the uses of triphala with other herbs and constituents for management of various conditions of the body. Other medicinal systems also talk about the miraculous effects of this remedy as in Tibetan medicine; there is a depiction of a blue Buddha holding a bowl in his right hand, which consists of the fruit of myrobalan (*Terminalia chebula*);

it was considered the symbol of good healing, describing its presumed health providing powers whereas the juice of this fruit was famous as ambrosia (godly food or drink of immortality) for enhancing the expectancy of life (Dakpa, 2014).

In a prehistoric time when the Arab peoples conducted trade with India, they introduced pepper, cardamom, cinnamon and other spices to Europe. This trade was means of introducing several Indian drugs to Greek medicines; when Alexander the Great entered and occupied India, numerous Greek doctors in his camp learned about the Indian medicinal system and gathered a considerable understanding of information from people living in that region and Vaids of India, then familiarised them in their motherland on their remigration to home. The three myrobalans were therefore made known to the Greeks; various texts and manuscripts on Unani medicine stated that those medicines were brought from India, and the trio is recognised as *itrifal* in Greco-Arabic medicine (an Arabised form of triphala) originated from the word triphala (three fruits) (Said, 1997). These three fruits are vital constituents of the formulation; numerous varieties of *itrifal* are popular in Greco-Arabic medicine, the most famous amongst them that has been consumed for numerous decades being *itrifal saghir* (Mahdihassan, 1978). In the canon of medicine (inscribed by Avicenna) the *itrifal saghir* was advised for gastric relaxation, non-bleeding piles, to decrease the accumulation of excessive fluids and moisture in the stomach (Avicenna et al., 1999; Kamali et al., 2012). The bodily humours or *tridoshas* are required to be in a state of balance for functioning optimally, and any variations can upset the health and regular functioning of the person. The equilibrium in *tridosha* is extremely sensitive and is inclined to deviate because of environmental modifications, i.e. seasonal variations, age of the person and transformed lifestyle (physical activity, alterations in habits of food) (Puri, 2003). This composition (triphala) is recognised to maintain the consistency of all three bodily humours/*doshas*, enhance the immunity of a person, aid in tissue rejuvenation and cease senescence (Caraka et al., 2001). Triphala's specific constituents alleviate the three *doshas*; the *pitta* by *Emblica officinalis*, *vata* by *Terminalia chebula* and *kapha* by *Terminalia bellirica* (Pandey, 2001).

In Ayurveda and Greco-Arabic medicine, triphala or *itrifal* is consumed for several diseases depending on one of the three bodily humours—for instance, it tones up the gastrointestinal tract, cleanses the digestive tract, including the intestines, supports the digestion of food, prevents constipation, reduces or maintains the level of cholesterols in blood, makes the circulation better, increases the peristaltic movements of the intestine, protects the kidneys and also acts as a hepatoprotective agent (Baliga et al., 2012; Mukherjee et al., 2006). Triphala is available in a number of dosage forms, including *itrifal* (semi-solid form), *kwatha* (decoction), *churna* (powder form), *taila* (oil), *mashi* (ash), or triphala ghee or *ghrita*, determined by the situation and disease of the patient (Baliga et al., 2015). Oil of *Ricinus communis* consumed with triphala decoction magnifies its strength twice, whereas in old age, in infants or in individuals who are affected by any other serious disease, triphala can be advised with extracts of meat or milk for managing constipation (Bhishagratna, 2014).

Rasayana

Rasayana are the agents that prolong ageing, heal physical and mental ailments, intensify intellectual power, improve vision, help in the appropriate digestion of food,

vitalise energies of the body, generate power, improve memory and make complexion flawless. Rasayana can modify the body's metabolism in numerous manners so that the body tissues can significantly deal with a variety of roles, from the nourishment of food to elimination. A number of these herbal medicines remove toxins and other waste materials from the body through the liver, kidney, skin and lungs, whereas others work by encouraging gastrointestinal functions and as antibacterial agents. Some Rasayana also aid in the clearance of *ama* (a waste product) (Puri, 2003). Rasayana are helpful to individuals regardless of their sex, age or cultural tradition. They improve all phases of physiology and preserve the body's strength, youthfulness, vitality and stamina. These herbs have the most crucial character in escalating liveliness and keeping illnesses away. The advantages of taking Rasayana herbs are progressive with consistency and time, and the herbs are usually of minimum or no side effects even when consumed for unlimited time (Caraka et al., 2001). Among all preparations of Rasayana, triphala is the easiest one with each one of the myrobalans and the blend having Rasayana properties (Baliga et al., 2012; Jagetia et al., 2002; Mukherjee et al., 2006). Among three of the myrobalans, *Emblica officinalis* have cooling, whereas *Terminalia chebula* and *Terminalia belerica* have warming properties. Being a mixture of all three, triphala is hence stable composition (Caraka, 1996; Suśruta & Kunja Lal, 2006).

Phytochemical Constituents of Triphala and Their Effects on Health

The most important chemical constituents in the formulation of triphala are gallic acid, tannins, chebulinic acid, ellagic acid, flavonoids, fatty acids, amino acids, anthraquinones and numerous carbohydrates (Belapurkar et al., 2014; Lee et al., 2005; Lu et al., 2012). HPLC has discovered ellagic acid, gallic acid and chebulinic acid to be the chief constituents of triphala (Lu et al., 2012). Triphala-originated polyphenols, for instance, chebulinic acid, are also converted by the microbiota of the human gastrointestinal tract into bioactive metabolites, which have exhibited promising in vitro activities to avert oxidative destruction (Olennikov et al., 2015). A few of the groups of phytochemical constituents and their health benefits are discussed next.

> *Tannins*: Tannins are occasionally recognised by the name of phyto polyphenols. These polyphenols have astringent properties. Certain constituents are present in numerous plants and have the tendency to prevent various illnesses. Many human biological activities, such as tumour promotion inhibitory activity, anticarcinogenic activity, antioxidant and antimicrobial activity, are actively found in tannins. The anti-infective activity might be because of their capability to incapacitate the adhesion of microorganisms (Okuda & Ito, 2011).

Flavones, flavonoids and flavonols: Flavonoids are generally recognised as secondary metabolites of plants that consist of the aromatic ring (Kumar & Pandey, 2013). Flavonoids and numerous other phenolic constituents have been known for their efficient anti-oncogenic, anti-inflammatory, antioxidant, antimicrobial and immunity-boosting activities. Moreover, they protect skin from ultraviolet radiation and have cardio-protective effects (Tungmunnithum et al., 2018). Amusingly,

an enormous number of phenolic and flavonoids show antimicrobial effects; they have also been mentioned as an antimicrobial agent against *Propionibacterium* acnes, which are the most common cause of acne. Researchers also proposed that the rise in anticancer activity was associated with the intensification in the number of polyphenolic constituents (Danciu et al., 2015). Quercetin is a remarkable anticancer against breast and prostate carcinomas (Brusselmans et al., 2005; Kumar & Pandey, 2013). A massive number of phenolic compounds and flavonoids have been verified for their significant effects on inflammatory activities and functions of the immune system (Locatelli et al., 2018; Middleton & Kandaswami, 1992). Apigenin, quercetin, luteolin and hesperidin were testified as flavonoids consisting of prospective anti-inflammatory effects (Kumar & Pandey, 2013). Constituents of plant chemicals, particularly flavonoids and phenolics, is one of the most remarkable choices that show favourable outcomes on ultraviolet-irradiated skin (Saewan & Jimtaisong, 2013; Svobodova et al., 2003). Quercitin's local use efficiently inhibited ultraviolet-B-prompted skin destruction in hairless rodents (Casagrande et al., 2006).

Ellagic acid: Ellagic acid (the polyphenol) is usually present in numerous vegetables and fruits, including pomegranates, cranberries, blackberries, strawberries, raspberries, pecans, walnuts, and other organic food. Ellagic acid holds anticarcinogenic, antioxidant and antimutagenic properties and is also stated to have antifibrotic outcomes; therefore, it helps prevent ALD (alcoholic liver disease) (Baliga et al., 2019).

Quinones: Quinones may lead to deactivation of the protein and functional loss in microbial cells. There is a tremendous antimicrobial effect in a variety of quinones (Cowan, 1999).

Vitamin C: All three constituents of triphala consist of vitamin C; however, the *Phyllanthus emblica* comprises the highest amount of vitamin C, and when it is combined with the other two myrobalans, the nutritional quality of vitamin C is enhanced. Vitamin C deficiency can cause bleeding gums while an adequate dose can prevent scurvy and other diseases of the gums; moreover, vitamin C exhibits potent antioxidant activities. Also, vitamin C, in conjunction with flavonoids, assists in accelerating the process of healing (Naiktari et al., 2014).

Gallic acid: Gallic acid is also found in all three myrobalans of triphala. Gallic acid has immunostimulatory and antioxidant properties (Belapurkar et al., 2014). Moreover, gallic acid subdues the growth of malignant cells (Mukherjee et al., 2006).

Pharmacological Benefits of Triphala

Studies have confirmed several potential benefits of triphala, which comprise free radical hunting, anti-inflammatory, antioxidant, immune-stimulating, pain alleviating, cicatrizant, gastric hyperacidity decreasing, appetite-stimulating, chemopreventive, antibacterial, dental caries preventing, antipyretic, high blood glucose reducing, antistress, adaptogenic, hepatoprotective and radioprotective effects. The composition of triphala may also encourage appropriate assimilation and absorption of food, decrease cholesterol levels in serum, make the circulation better, relax bile ducts, prevent gradual weakening of the immune system and enhance the production

of haemoglobin and RBCs. These myrobalans preserve the process of homeostasis in the endocrine system (Baliga et al., 2012). Triphala has been established to have a radioprotective influence in rats susceptible to γ radiation (Jagetia et al., 2002). Each herb utilised in this composition has numerous other health advantages, such as *Terminalia chebula* having anticancer, antimutagenic, antimicrobial and anti–dental caries properties and reducing confined anaphylaxis. *Emblica officinalis* has cytoprotective, anti-inflammatory, antimutagenic, gastroprotective, antioxidant and hypolipidemic activity. Similarly, *Terminalia belerica* is described to work as a hepatoprotective agent, protect against necrosis of cardiac muscles and diminish fat-stimulated atherosclerosis (Mukherjee et al., 2006).

Role of Triphala in Infectious Diseases

Preclinical development or non-clinical trials have revealed that triphala and all three of its ingredients have considerable antimicrobial effects against a range of disease-causing infectious agents. Some of the trials have demonstrated that the ethanol and aqueous extracts of the single constituents, as well as powder of triphala, have noteworthy antimicrobial activity against the culture of organisms acquired from the infected patients of human immunodeficiency viruses, with the most satisfactory effects being noted in the ethanol contrasted with aqueous extracts (Srikumar et al., 2007). Another research project displayed that the water-based and ethanolic extracts of triphala were also influential on clinical isolates and that the water-based extract was superior to the ethanolic extract on *Staphylococcus aureus*, *Escherichia coli* and also against those isolates that have developed resilience against the antibiotic (Biradar et al., 2008). A current report on the HAE of triphala also proposes that it was active against MDR uropathogenic microorganisms. All these analyses and statements collectively specified triphala's efficacy as a new antimicrobial and least harmful agent (Bag et al., 2013). Triphala also acts as an antiviral agent against herpes simplex virus 1, swine flu, hepatitis B virus or cytomegalovirus (Tarasiuk et al., 2018).

Cholesterol-Reducing Effects of Triphala

Triphala decreased the levels of free fatty acids, total cholesterol, LDL and VLDL in mice fed with a cholesterol-rich diet for 48 days (Saravanan et al., 2007). Another study (Manjunatha et al., 2001) revealed that the study participants who received 500 mg powder of *Emblica officinalis* per day for up to four months had considerably improved glucose tolerance, diminished cholesterol levels and an improved ratio of high-density and low-density lipoproteins in contrast with the participants of a control group who were getting 500 mg of vitamin C per day. The cholesterol-reducing and anti-atherogenic effects of *Emblica officinalis* were also analysed in rabbits fed with a diet that stimulates fat accumulation in the arteries. Subsequently, 60 days of supplementation with *Emblica officinalis* decreased triglyceride levels, phospholipids, serum cholesterol and low-density lipoprotein by 66, 77, 82 and 90%, respectively. The animals that were treated with *Emblica officinalis* showed a reverted aortic plaque which proposed a strong hypolipidemic effect of *Emblica officinalis* (Mathur et al., 1996).

Triphala in Dental Diseases

Triphala aids in preventing and managing various periodontal diseases, including scurvy, dental caries and halitosis. Various research studies have revealed that triphala decreased the MMP-9 (matrix metalloproteinase-9) activity of white blood cells or granular leucocytes demonstrated in adult patients with periodontitis more efficiently than the antibiotic doxycycline, which was used in the control group (Abraham et al., 2005). Further research studies in humans have revealed that 6% of triphala was as efficient as 0.1% of chlorhexidine for the prevention of dental caries (Tandon et al., 2010).

Role of Triphala in Hyperglycemia

In vitro studies of triphala extract have revealed considerable antioxidant and blood sugar–reducing activities in diabetic rodents (Sabu & Kuttan, 2002). Another study showed that 90 mg per kilogram of triphala (orally) had substantial hypoglycemic effects (Puri, 2003). Triphala plays a significant role in reducing the absorption and assimilation of polysaccharides, diminishing the after-meal rise in blood glucose levels similar to that of new pharmaceutical preparations, such as acarbose and miglitol. Additionally, Triphala also reduced blood glucose levels in alloxan-instigated diabetic and normal rodents (Patel et al., 2012). A research trial conducted on patients with NIDDM discovered that triphala powder was given in a dosage of 5 grams for around 1.5 months, considerably reducing blood glucose levels (Rajan & Antony, 2008). A research study by Phetkate et al. (2012) discovered that flavonoids drawn out from *Emblica officinalis* showed potent hypoglycemic and hypolipidemic activities and escalated haemoglobin levels in rodents.

Triphala in Gastrointestinal Disorders

Triphala is consumed frequently in Ayurvedic and Greco-Arabic medicine as a mainstay of gastrointestinal management. Triphala is acknowledged to put forth antimicrobial action against a range of gram-negative and gram-positive microbes, for instance, *Streptococcus mutans* (typically established between end-to-end teeth or in the deep gaps of teeth) and *H. pylori* (the primary cause of irritation in the mucosa of the stomach and small intestine) (Tarasiuk et al., 2018). One research study analysed (Mehmood et al., 2013) the in vivo effects of *Emblica officinalis* in conditions of indigestion and constipation; the experiment reported that *Emblica officinalis* holds purgative and prokinetic activities.

One of the 2009 studies proposed to assess the intestinal protective effect of triphala preparations in methotrexate-stimulated deteriorating effects in rodents. It was proposed that the unbalanced composition of the triphala ingredients, i.e. the highest ratio of *Emblica officinalis*, protects the cellular membrane protrusions of the intestine better instead of its similar composition (Nariya et al., 2009). It has also been revealed that the prolonged treatment with triphala improved the incidence, number and viscosity of stools evacuated each day and reduced the distension and abdominal pain in healthy cases versus control persons who did not get triphala. The study implied that triphala could be recommended as the first-line treatment

for cases with impeded gastrointestinal motility, and in numerous other research projects, it has been mentioned that the existence of such beneficial plant chemicals in triphala, for instance, flavonoids, alkaloids, tannins, and terpenes, could be accountable for the antisecretory, antidiarrheal and spasmolytic effects of triphala (Mehmood et al., 2011; Mukherjee et al., 2006). It has been acknowledged that plant chemicals in triphala, such as gallic acid and quercetin, stimulate the growth of *Lactobacillus* and *Bifidobacterium* species while preventing detrimental gut microorganisms in the gastrointestinal tract such as *Escherichia coli*.

Moreover, the *Lactobacillus* bacteria have the enzymatic activity to reduce phytotannins such as gallic acid confined in triphala (Peterson et al., 2017). Other triphala-originated polyphenols, for instance, chebulinic acid, are changed by the microbiota of the human gut into metabolites, for example, urolithins, which can avert oxidative damage (Olennikov et al., 2015).

Triphala in Inflammatory Conditions

Long-lasting inflammation is harmful and impacts the health status of the body (Furman et al., 2019). Triphala has been known as a prospective anti-inflammatory agent. One study revealed that triphala acted more efficiently or similarly to standard anti-inflammatory drugs for many biochemical quantifications of inflammation (Rasool & Sabina, 2007). Additionally, triphala considerably decreased inflammatory indicators along with degradation of cartilage and bone in arthritic rodents (Kalaiselvan & Rasool, 2015).

Triphala in Obesity

In one of the randomised controlled trials conducted for up to three months, one group was treated with triphala while another group was given a placebo. The research participants treated with triphala lost approximately 5 kilograms of weight compared to the placebo group (Peterson et al., 2017). Another study revealed that triphala reduced the measurements of body weight and body fat in obese rodents, amongst which triphala was administered for up to 2.5 months; the composition also assisted in decreasing the levels of LDL, triglycerides and total cholesterol in the experimental group (Gurjar et al., 2012). Paranjape et al. advised 250 mg of triphala *guggul* before a meal with lukewarm water thrice a day for up to 12 weeks to reduce weight. Moreover, it decreases the total serum cholesterol, triglycerides, waist and hip circumference (Paranjpe et al., 1990).

Immunostimulatory Activities of Triphala

Some medicinal plants have dynamic phytoconstituents that can control the immune system by working together with the immunity-providing cells. Such chemical constituents regulate the physiological mechanisms and may play a vital role in increasing the body's resistance to a range of ailments and may enhance memory, which balances the individual's overall health. Similarly, the extract of *Terminalia chebula* demonstrates protective effects in rats through its immunomodulatory activity against

typhoid infection. *Terminalia chebula* is stated to be an efficient antimicrobial agent against numerous gram-positive and gram-negative microbes (Ghosh et al., 2008; Nagar et al., 2011); chebulic myrobalan also possesses antifungal properties against a range of fungal infections (Dutta et al., 1998) and antiviral properties against herpes simplex virus, swine influenza virus and cytomegalovirus (Yukawa et al., 1996). Similarly, *Terminalia belerica* and *Emblica officinalis* also effectively work against numerous infectious agents and various diseases. Triphala's composition not only protects the body from infectious diseases but also works against reactive oxygen species, free radicals and cancer-producing agents in the body. Triphala also works to manage several autoimmune diseases in the Ayurvedic and Greco-Arabic systems of medicines. The presence of multiple active constituents in all three ingredients, such as flavonoids, tannins, phenols and ascorbic acid, are accountable for triphala's potent immunosuppressant and immunostimulatory activities, determining it as a powerful plant-based immunomodulator (Belapurkar et al., 2014).

Triphala in Wound Healing

As the people started getting older, their healing powers began to decrease, i.e. remediation of wounds was also impeded; this might enhance the threat of numerous problems such as secondary infections. Research studies on animals, including rodents, revealed that the ointment of triphala extract was proven to be efficient in stimulating the healing of entire-thickness of skin wounds in both infected and clean conditions. Local use of triphala ointment decreased microbial counts and enhanced wound healing by inhibiting matrix metalloproteinase (MMP) expression, escalating wound closure and increasing superoxide dismutase, collagen, hexosamine and uronic acid levels (Kumar et al., 2008).

Cancer-Preventing Activities of Triphala

Triphala demonstrates anti-proliferative effects on cancer cells in both animals and humans. The extract of triphala consists of various phenolic constituents that are proven to be capable of suppressing the multiplication of cancer cells and inducing the death of cancer cells in the human colon, making it worthy of more research as a plant-based anticancer treatment (Vadde et al., 2015). Gallic acid in triphala has anticarcinogenic activity, especially when it comes to prostate malignant cells (Russell et al., 2011). Mouth wash consisting of triphala may aid to reverse tobacco-instigated pre-cancerous lesions of the mouth (Deshpande et al., 2014). Various research projects have also revealed that it can destroy cancer cells, but it does not affect the body's healthy cells, verifying it as a prospective anticancer remedy (Sandhya et al., 2006). Throughout management in pre-cancerous wounds like leukoplakia (Biradar et al., 2008), triphala is established to have considerable potential for reversal of these injuries.

Stress-Reducing Activities of Triphala

Several diseases are caused or aggravated by stress, such as anxiety, which amounts to being the foremost cause of disability globally (Peterson et al., 2017). Stress is

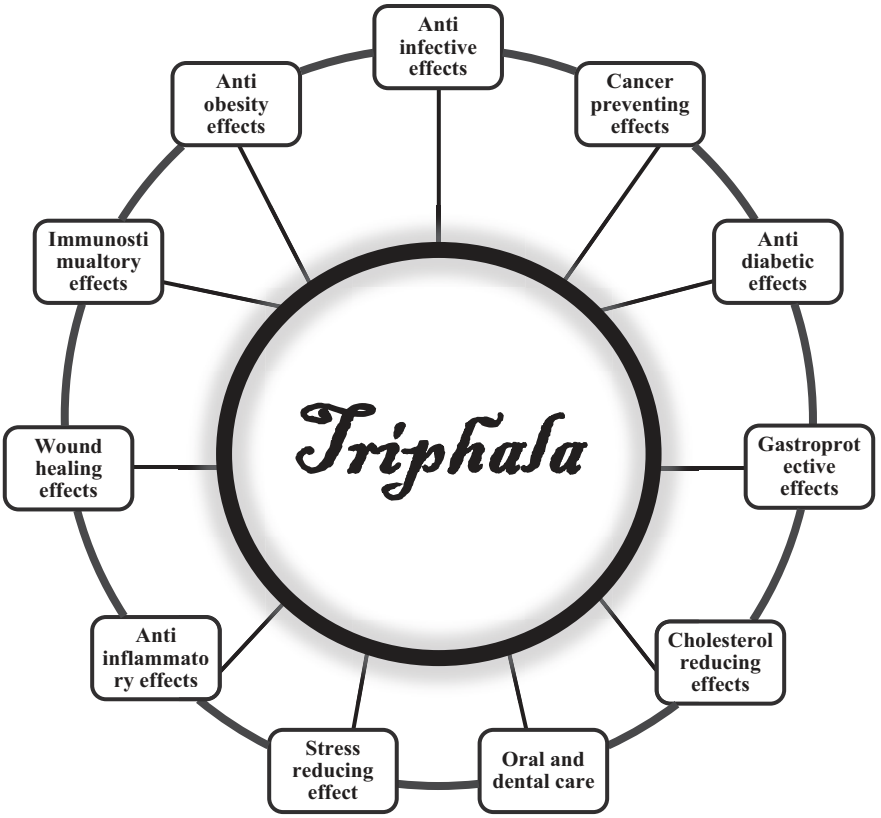

Figure 24.3 Pharmacological benefits of triphala.

considered the state of discordance initiated by any recognised threat responded to by an adaptive reaction to regenerate homeostasis and is related to numerous chronic ailments. Research studies conducted on animals have revealed that triphala defended against stress stimulated by cold and reversed all those biochemical and behavioural changes induced by stress, such as a rise in corticosterone and lipid peroxidation levels (Dhanalakshmi et al., 2007). Triphala also protected against the stress that is prompted by noise. Due to the busy schedule, increased workload, lack of exercise and changed lifestyle of everyone, contemporary humans undergo extraordinary stress levels; therefore, adaptogenic treatment modalities are required in clinical practice more extensively (Srikumar et al., 2006) (Figure 24.3).

Conclusion

Triphala is proven to be effective in all kinds of diseases, including carcinogenesis and malignancies. Moreover, triphala enhances the intellectual abilities of individuals. Although it cannot be a substitute for contemporary medicine, especially antibiotics, triphala can be given in conjunction with modern medicine to enhance its efficacy and improve overall health without any severe adverse reaction. Further

comparative studies are still needed in time to verify its miraculous effects in certain diseases, especially metabolic and lifestyle disorders.

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