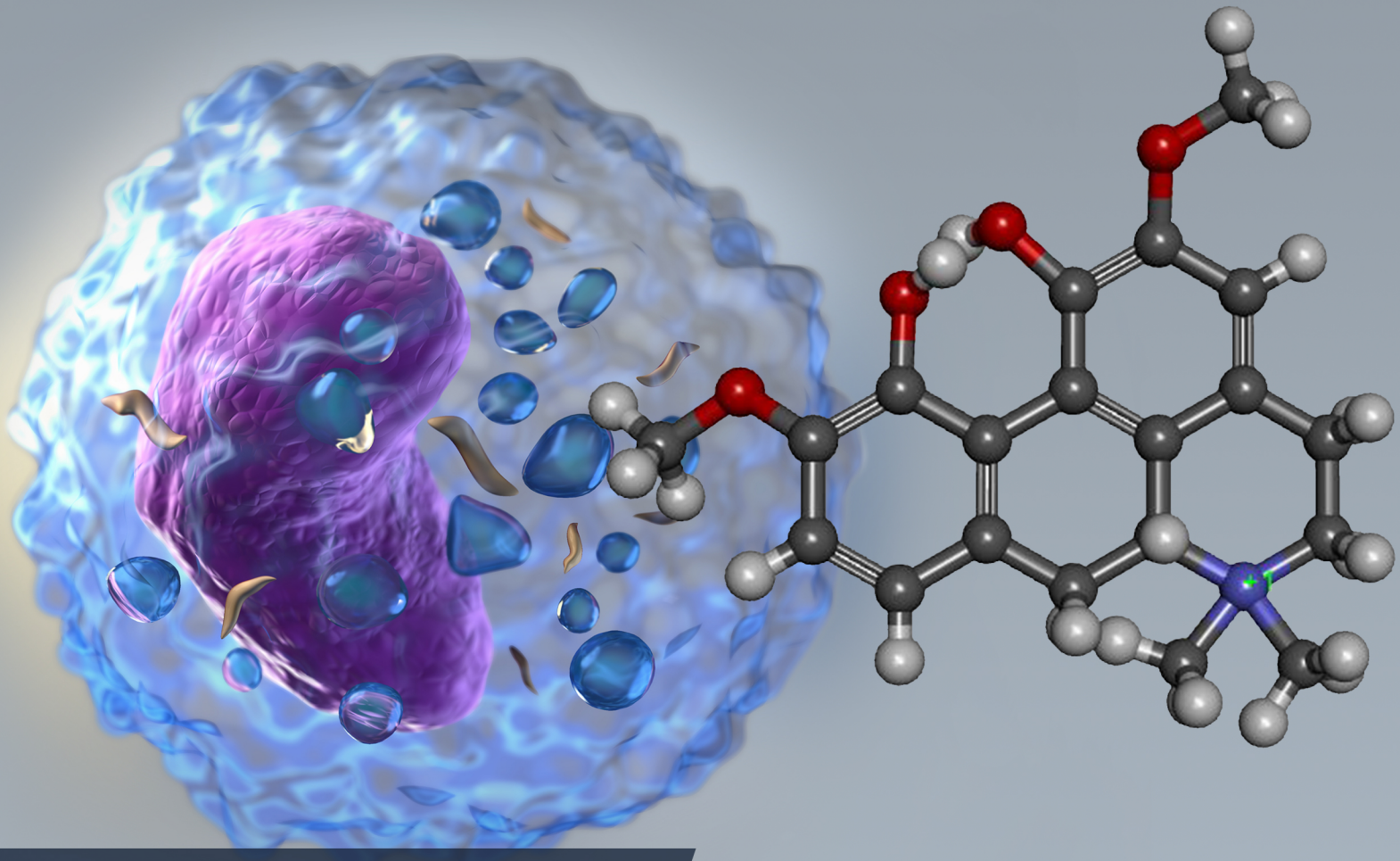
NATURAL IMMUNOMODULATORS: PROMISING THERAPY FOR DISEASE MANAGEMENT



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Natural Immunomodulators: Promising Therapy for Disease Management

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PREFACE 1

Immunomodulatory drugs, of both natural and synthetic origin, are increasingly being researched & developed for the treatment of human diseases, together with inflammatory disorders. In the post-SARS-CoV-2 pandemic of 2020, the research in immunomodulators has been found to be increased. The significance of such compounds, which focus on modulation of our immune status over remedial drugs, has been realized. Regardless of its extraordinary efficiency and specificity, the distortion of immune responses can be accountable for several disorders, such as autoimmune diseases, allergies, immunosuppression, and AIDS. Immunomodulators play a key role in diming such disorders too. In the past ten years (2011 to 2021), there have been several hundred reviews either on immunomodulators or combined with vaccines and adjuvants. However, a comprehensive book exclusively on all aspects of immunomodulators was needed for the clinicians, researchers, and Pharma & Biopharma professionals. Eminent and well-experienced professors, researchers, bioscience industry professionals, and technologists from India congregate to review this in the form of a comprehensive book. The book with the title "Natural Immunomodulators: promising therapy for disease management" encompasses all aspects such as ways of modulating immunity, diseases & disorders related to immunity, natural & synthetic immunomodulators, related analytical techniques, bioassays, and other methods for immunomodulators in the preclinical and clinical setting, delivery of immunomodulators: challenges and novel approaches, marketing strategy and regulatory perspectives, future path, and perspectives, *etc*. A glance through the twelve chapters reveals the vastness of the work on immunomodulators and their significance for mankind. The content of the book is like a crisp encyclopedia on the topic. The distinguished editorial team has refined the content to make it a ready one-stop reference for researchers, investors, bioscience & biotech professionals, vaccine developers, students, clinicians, *etc*. All the authors with decades of proficiency in the medical and clinical field put all their best effort to encompass the key literature in the past two decades along with representative historical aspects. I look upon this book as a high-impact reference.

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PREFACE 2

With the advancement and rapidly changing technology, information is accumulating in ever intimidating quantities with facts and figures that give logical reasoning, simple explanations about chaotic mechanisms, and the complexity of biology and life. Scientific knowledge is full of paradoxes, and with the addition of new information, it becomes easy and simple to unravel the unknown to known with rational justification.

Our book, entitled Natural Immunomodulators: promising therapy for disease management, is a small effort to gather recent updates in the field of immunology, pathology, and immunomodulatory therapies intended at harnessing the power of nature. Although the information is ever expanding in volume, we have taken intense efforts to conceptualize and summarize the information that emphasizes the significance of natural immunomodulators.

The immune system complexity is secondary to the nervous and endocrine systems. The immune system has a profound impact and involvement in emerging lifestyle-related chronic illnesses and infectious diseases. The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the year 2019 had underscored the significance of immunity. Moreover, the recent discovery of the brain lymphatic system in 2015 had stated the linkages of the immune system in neuropathology.

Our book provides a preview of the immune system and every aspect of natural immunomodulators, including their natural sources, standardization, novel drug delivery methods, marketing, regulatory requirements, challenges, and limitations to get them in mainstream in line with and parallel to modern medicines. The retrieved scientific information from literature is presented comprehensively without losing the essence of the research to readers, and the content is abstracted succinctly in simple, lucid language.

The successful completion of our book was possible due to the collective efforts and support from chapter authors, our research students, friends, and colleagues. We thank all of them for their sincere contributions in shaping this book. Finally, we are also grateful to the Bentham publishing team for their outstanding support and cooperation.

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CHAPTER 1

Introduction: Immune System & Modulation of Immune System

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Abstract: The immune system is a complex, intricate organ system with features like flexibility, recognition, discriminating potential between self from non-self, and memory to defeat notorious external and internal threats to human health functioning. Innate immunity is inborn, and acquired immunity develops through secondary education; they are interconnected, interdependent, and execute tasks with bi-directional communications. A deeper understanding of immune biology revealed a remarkable contribution of the immune system in several chronic illnesses, and has taken a central stage in pathophysiology. In essence, the weakened or overactivated immune system leads to these chronic illnesses. Modulation of the immune system is an efficient and valid approach to prevent the underlying pathophysiology of such diseases. A gamut of natural immunomodulators targeted at specific or non-specif immune cells has delineated their potential to achieve the equilibrated and balanced immune system. Preclinical and clinical studies demonstrated the implication of microbiota, nutrients, natural herbs, and micronutrients for immunostasis. The immune system's complexity, its close association with the endocrine and nervous system, target identification, and convenient, reliable tools to assess immune function and modulation are a few limitations that hampered the attainment of immunostasis. Despite these limitations, novel therapies targeted at immunomodulation in chronic diseases are promising and paving the future path to novel therapeutics.

Keywords: Adaptive Immunity, Immune System, Innate Immunity, Immunomodulation.

INTRODUCTION

The principal components of the immune system are innate and adaptive immunity. The immune system is an older system on the evolutionary scale, and among

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the two, the innate immune system is the ancestral one, present in both invertebrates and vertebrates [1]. The innate system is considered as the first line of defense for invading infection, growing neoplastic cells, or any other foreign matter in the body. The innate system lacks clonal expansion, memory, and antibodies and does not respond to changes in external stimuli. The innate system reacts and responds through its receptors to highly conserved microbial proteins like lipoteichoic acids and lipopolysaccharide of gram-negative and gram-positive bacteria, respectively [2, 3].

Immunity is the mechanism by which the body protects itself against diverse environmental agents, such as microorganisms or their product lines, food, chemical products, drugs, and pollen grains. The word 'Immunity' originated from the Latin word 'Immunis', which means 'exempt from public services' (from im-, in- not, un-, without+munus duty, task, service). The very first term was introduced in B.C. 430 during the plague of Athens. Thucydides noticed that people who had managed to recover from a prior bout of the disease were capable of treating the sick without becoming sick on the second contact [4]. Later Rhazes (880-932) termed the immunity as acquired immunity with an explanation of excess moisture being expelled from the blood and therefore preventing the subsequent occurrence of the disease. This theory explains the term acquired immunity as smallpox bout was effective in protecting its survivors from future infections and explains several terms about smallpox known during the 10^{th} century. Louris Pasteur reconfirmed these observations in his germ theory of disease [5], which were later proven by Robert Koch in 1891 and awarded with Nobel prize. In the 19^{th} century, Paul Ehrlich had a substantial contribution to immunology by proposing the side-chain theory, explaining the specificity of the antigen-antibody reaction.

The immune system can be defined as the bodily system that produces the immune response to protect the body from foreign materials, cells, and tissues. It is the body's defense mechanism to render foreign antigens and disease-causing bacteria from entering the body. It never attacks commensal flora that inhabits the gut, skin, and other tissues to the host's benefit and always differentiates between individual own cells and other harmful invading cells. All animals have nearly the same immune system, but it varies within individuals. It varies as a consequence of heritable and non-heritable influences [6].

COMPONENTS OF THE IMMUNE SYSTEM

Immune system differs from other systems in the body, as the cells involved in the system are highly motile. It specifically uses the blood vessels and lymphatic vessels to reach the infection site in order to move in and out of the lymphatic tissue.

Though the immune system is found all over the body, it still contains some specialized organs, which regulate the immune response and are capable of rapidly producing numerous cells that can stop spreading infection. Immune cells present in the reservoir can penetrate any cells in the body to combat the invasion. All the cells in the body originate from hematopoietic stem cells in the bone marrow as a precursor, but their site of origin and residence differ from each other [7]. The thymus and bone marrow are primary immune organs. Secondary immune organs include the lymph nodes, spleen, Peyer's patches, appendix, tonsil, adenoids and other mucosal-associated lymphoid tissue (MALT) [8] Fig.(**1**).

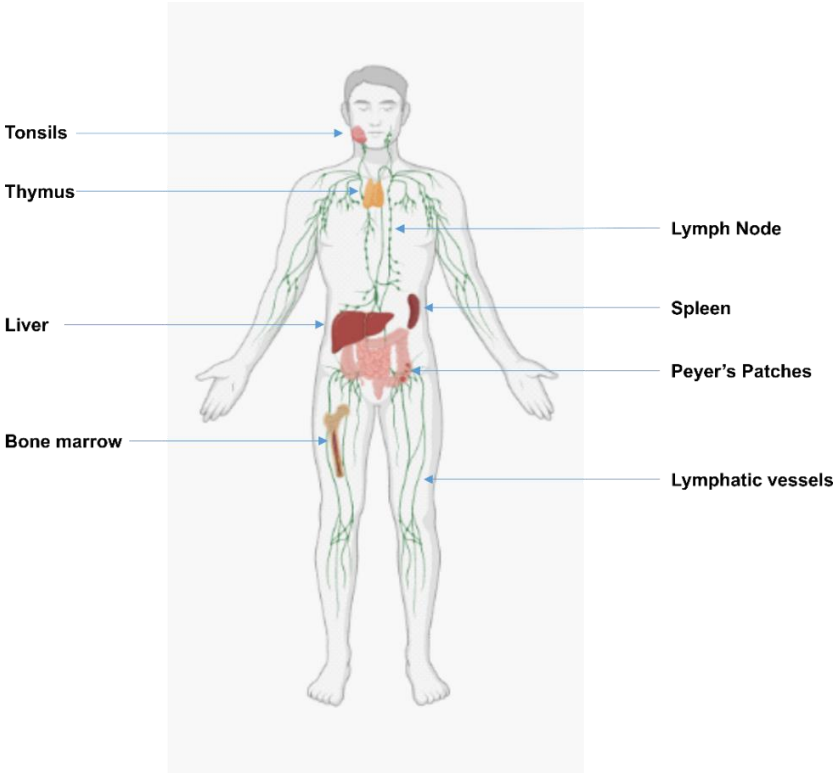

Fig. (1). Primary and secondary immune organs of human body.

Bone Marrow

It is the primary site for blood cell synthesis. It gives rise to all types of precursor blood cells. Red bone marrow is a connective tissue that is highly vascularized, having 0.05 to 0.1% pluripotent stem cells derived from mesenchyme. These cells proliferate; differentiate into lymphoid and myeloid stem cells, which give rise to lymphocytes and myeloid cells, respectively. These stem cells further differentiate and become committed progenitor cells, which give rise to specific blood cell types. Some progenitor cells are also referred to as colony-forming units (CFU)

CHAPTER 2

Diseases and Disorders Associated with Immune System

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Abstract: The human immune system is one of the complex systems of the body, which works against both external and internal invasion. It has two parts: the innate and the acquired immune systems. We have been born with the innate system which gives a quick response for the invading pathogen non-specifically. To deal with the typical environmental antigens, immune system adapts to changes. The acquired (or adaptive) component develops over time and produces antibodies that "remember" invaders to fight them if they return. Failure of it could be due to genetic defect (weak natural immunity), inability to adapt to the change, hyper-responsiveness, or inability to distinguish self from foreign, leading to various diseases and disorders. Various genetic defects of the immune system are at the core of Primary Immune disorders (PIDs), while overactivity is responsible for allergic diseases. Autoimmune diseases are mostly due to malfunction of the adaptive immune system, while in Systemic Auto-inflammatory Disorders (SAIDs), the innate immune system is affected. Advancements in technology and genetics have improved our understanding of the pathogenesis, diagnosis, and management of these diseases.

Keywords: Autoimmunity, Allergic Diseases, Auto-inflammation, Cancer Immunotherapy, Immunological Disorders, Immunodeficiency, Neuro-immune System.

INTRODUCTION

The immune system is an efficient complex network of cellular elements, molecules, and pathways that is evolved to protect the host or multicellular organisms against external offends or invaders, and its balance functioning is essential to avoid the development of various disorders. In a normal infectious state, the infectious agent activates the innate immune response, which causes symptoms followed by an adaptive immune response that leads to clear infections

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and develops a protective immunity state. But in several circumstances, this will not happen, and there can be a failure of the host Immune response against the invasive agents. The failure of the host immune system can be due to avoidance of a normal immune response by pathogens; genetic defects give rise to failures of defence mechanisms, immunodeficiency syndromes, autoimmunity, allergic responses, *etc.* The prevalence of Immune disorders is on the rise, as many new rare disorders have been identified in the last few decades. Autoimmune Diseases (ADs) account for about 3–5% of the world population, whereas a 30 to 40% rise in allergic disorders is seen. Major advancements in technology and genetics have improved our understanding of the pathogenesis, diagnosis, and management of these diseases [1 - 3].

CLASSIFICATION OF IMMUNE DISEASES AND DISORDERS

When we talk about immunological diseases and immunological disorders, we can sketch a marked line between these two terms. The term immunological disease is ascribed to the situation in which the part, organ, or organ systems of the body get affected by various internal or external factors, whereas immunological disorders are characterized by irregularity or failure of organ function or organ system. The immunological disorders can be physical, structural, genetic, and behavioural. The immune diseases and disorders can be classified based on Organ-specific and organ-non-specific, or we can classify them as Phenotypic diseases or disorders according to the Inborn Errors of Immunity Committee (IEIC). The immune system works for the protection of the body.

BROAD CLASSIFICATION OF IMMUNE DISEASES AND DISORDERS

I. Immunodeficiency disorders
II. Allergic/ Hypersensitivity reactions
III. Autoimmune disorders
IV. Auto-inflammatory disorders

Immunodeficiencies (IDs)

A person with immune deficiency syndromes has lost the ability of one or more components of the immune system to respond protectively to a pathogen. Immunodeficiencies (IDs) are a group of diseases with alterations in either inborn or adaptive immune responses. They are classified as primary when of genetic origin, more recently called inborn errors of immunity (IEI), and secondary when they are acquired [4]. Primary immunodeficiencies (PIDs) include approximately 420 monogenic diseases that are more susceptible to infections and non-infectious complications, including allergies, malignancies and autoimmune diseases (ADs),

which also include developmental disorders, autism, intellectual disability, epilepsy, gastroenteropathies, pneumopathies, dermatoses, skeletal and renal abnormalities [5]. There are two types of PIDS. Monogenic immunodeficiencies occur because of mutations in genes responsible for immunological tolerance, thus triggering autoimmunity, including poly-autoimmunity and polygenic immunodeficiencies with a complex pathophysiology and having a multifactorial etiology.

Classification of Immune Diseases and Disorders Based on Inborn Errors of Immunity

Inborn errors of immunity are also known as primary Immunodeficiencies. All types of inborn errors of immunity are compiled by the International Union of Immunological Societies Expert Committee. The important manifestations of primary immunodeficiency are the increased sensitivity to auto-inflammatory diseases, autoimmunity, and allergic diseases. According to the ISEC committee, primary Immunodeficiencies can be classified into 10 classes Table **1.**

Table 1. Classification of immunodeficiency disorders.

Immunodeficiency Disorders		
Class	**Subclass**	**Disease/Disorder**
Immunodeficiencies Affecting Cellular and Humoral Immunity	T-B+ severe combined immune deficiency (SCID)	i. CD45 deficiency ii. L7Rα deficiency iii. AK3 deficiency iv. Coronin-1A deficiency
	T-B- SCID	i. RAG deficiency ii. AK2 defect iii. DCLRE1C (Artemis) deficiency iv. DNA ligase IV deficiency v. Adenosine deaminase (ADA) deficiency
	Combined immunodeficiency (CID), generally less profound than SCID	i. CD40 ligand (CD154) deficiency ii. CD40 deficiency iii. D3γ deficiency iv. ICOS deficiency

CHAPTER 3

Natural Sources of Immunomodulators

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Abstract: Nature is replete with an arsenal of compounds that can be investigated for their therapeutic potential. The immune system involvement in severe chronic illnesses or emerging infectious diseases has provided clinical evidence. The prevention and treatment of these diseases targeted at the immune system with natural immunomodulators are gaining momentum, owing to their diverse array of activities. Treating acute illnesses with modern medicines has been successful; however, treating chronic illness treatment remains elusive and disappointing. Notably, this chapter reviews the natural resources of immunomodulators. Natural immunomodulators from plants, marine, and animals are of prime importance, and they possess many pharmacological activities. Similarly, microbiota modifiers - prebiotics, probiotics, and micronutrients- are imperative in restoring immune homeostasis. This chapter summarizes these natural immunomodulators and their power to boost immunity and human well-being.

Keywords: Alkaloids, Glycosides, Micronutrients, Microbiota, Natural Immunomodulators, Prebiotics, Probiotics.

INTRODUCTION

Immunopharmacology, the most upcoming and rapidly developing branch of pharmacology, deals with pharmacology, immunology and pathology. It holds considerable potential for the prophylaxis and treatment of various spectrum of immune system illnesses and disorders. The etiology and pathophysiology of many diseases are known to be influenced by the host's immune system's specific and non-specific defences. Almost every culture has a history of herbalism, depending on the natural flora and vegetation and evidence of harnessing the power of natural remedies to heal human diseases and disorders. Ayurveda (Ayu:

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(Ayu: Life Veda: Knowledge), 'the science of life, is the world's oldest system of medicine and has enlisted various indigenous herbal and herbo-mineral formulations (for example, Shilajit) for human well-being.

Regulation of immune response to alleviate illnesses has piqued interest for many years, and the Ayurvedic notion of Rasayana is built on similar concepts. Many factors, such as medications and stress hormones, can affect the immune system's function and efficiency, resulting in either immunostimulation or immunosuppression. The healthy state is thought to be the result of a complex fine-tuning of immunoregulatory mechanisms. Immunomodulators are agents that maintain the homeostasis of the host immune system either by immunostimulation or by immunosuppression.

In light of the current context where the emergence of viral diseases like AIDS, hepatitis, and Severe Acute Respiratory Syndrome CoronaVirus (SARS-CoV) are viewed, and host defenses are compromised, the concept of Rasayana in Ayurveda as we understand, it seems to be imperative as it elevates the host defenses. Immunomodulatory medications may be used in clinical settings to restore immunological insufficiency, as in AIDS and other viral diseases, or to reduce normal or excessive immune efficiency, as in transplant rejection and autoimmune disorders.

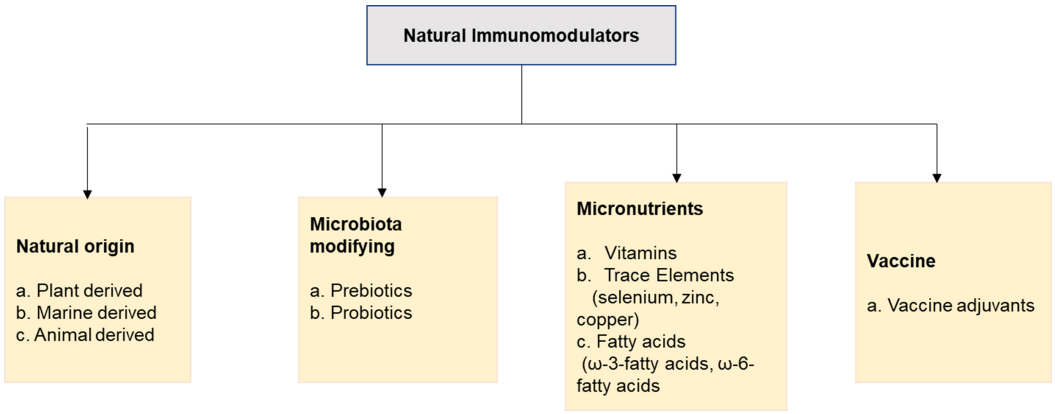

Fig. (1). Classification of natural immunomodulators.

The literature is replete with a plethora of natural immunomodulators derived from several sources like plants, animals and marines. The cross-talk between immune cells and natural microbial flora also has a significant role in immunity, and disturbed immune function can be corrected with the use of microbiota-modifying reagents like prebiotics and probiotics. Based on their sources and role,

natural immunomodulators are broadly classified into many groups, as depicted in Fig. (**1**) [1 - 4].

PLANTS AS SOURCE OF IMMUNOMODULATORS

Herbal medicine is one of the most ancient forms of remedial treatment evolving with humanity. A retrospection of the healing power of plants and a return to natural remedies is an absolute need of our times. Herbal medicine is based upon the principles that plants contain. As research on herbals continues, an increasing number of plants is becoming recognized as immunomodulators. Table **1** and Fig. (**2**).

Glycosides

These organic compounds from plant sources are degraded by enzymes, yielding one or even more glucose molecules. They are acetals, or sugar elixirs, which are formed when the hydroxy groups of glucose and non-sugar molecules come in contact with the loss of a hydroxyl group. A number of glycosides have been shown to have immunomodulatory properties. *Picrorhiza scrophulariiflora* iridoid glycosides [1] and *Andrographis paniculata* anthraquinone glycosides [2] are two examples of them. Dendroside A and dendronobilosides A and B, three novel sesquiterpene glycosides, have been identified in the stem of *Dendrobium nobile*, a plant used in traditional Chinese medicine. Dendroside A and dendronobilosides A were known to increase the proliferation of murine T and B lymphocytes *in vitro*, although dendronobiloside B inhibited it [5].

These are some of the widely spread organic compounds in plants, present as free-state glycosides. They are mostly made up of water-soluble chemicals. The carbon skeleton of their molecular structure is C6-C3-C6. Flavonoids are powerful water-soluble strong antioxidants as well as free radical scavengers that protect cells from oxidative damage. They also have great anti-cancer properties, which protect against all phases of carcinogens. Flavonoids in the blood have been related to a decreased risk of heart disease [5]. They impede the initiation, propagation, and advancement of malignancies in terms of anti-cancer action. Plant flavonoids, with chemoprotective agents, have recently garnered the attention of many researchers as a highly essential dietary supplement for people with cancer [6, 7].

Tannins

Tannins are amorphous, seldom crystalline compounds that are astringent and bitter in taste. They are soluble in water and alcohol. They are phenolic compounds, classified chemically based on the hydrolysis product.

CHAPTER 4

Standardization of Immunomodulator Natural Drugs

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Abstract: Natural medications are gaining popularity as people become more aware of their benefits and accept their use in modern medicine. Natural drugs have demonstrated extensive suitability as curative agents for various disorders due to their fewer side effects and toxicity. Scientists face a tremendous problem in developing accurate analytical techniques that can efficiently profile the contents of phytochemicals. This is in addition to quantitative studies of marker or bioactive chemicals and some other important ingredients. Natural medicines, on the other hand, lack standardized parameters. Standardization is a vital step towards the formation of a constant chemical profile, consistent biological activity, or just a quality assurance programme for the production and manufacturing of natural products. As a requirement for global harmonization, the WHO criteria for assessing the safety, efficacy, and quality of natural drugs are extremely important. Scientific research of some of the natural origin plants regarded in Ayurvedic Rasayana for their beneficial potential has generated good results. The number of plants with a potential immunomodulatory activity that has been cultivated using conventional or cell culture methods is standardized. This can help to portray and validate their usage in folk medicine in the early days, as well as give an establishment for future investigation. The goal of this chapter is to showcase the findings of research evidence on standardized natural plant-origin immunomodulators. The chapter also goes through biological screening strategies for diverse plant medications with the goal of revealing the immunomodulation mechanism. Researchers will hopefully be encouraged to pursue more research on medicinal plants with immunomodulatory potential as a result of this study.

Keywords: Immmunomodulators, Immunostimulants, Immunosuppressants, Natural Drugs, Plant Tissue Culture, Standardization.

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INTRODUCTION

Natural drugs are the use of plants and plant remedies in the prevention and control of diseases. Plants have been utilized medicinally by societies all over the globe for more than thousands of years and contains a primary resource of drugs throughout human history. The fact that they are still extensively used nowadays is not a relic of the Dark Ages, but rather a sign that natural-origins plants are becoming an element of current high-tech medicine. Natural drugs act as an imperative role in the scientific structures of a few countries, like Ayurvedic medicine in India and Traditional Chinese Medicine (TCM), which, along with various complementary therapies, are seeing renewed interest. Natural drugs are recognized by the WHO as an essential component of primary health care and are 3 to 4 times more widely used than traditional medicine worldwide. According to the WHO, traditional medicine is used by 65–80% of the worldwide population as a primary resource of healthcare, and 40% of the worldwide population relies directly on traditional medicine for healthcare (WHO, 2003). It has also been discovered that nearly 15,000 plant species out of 45,000 are used for their precise medicinal value, demonstrating the significant diversity of plant species [1, 2].

According to the report, more than 130 compounds derived from approximately 100 plant species can be considered important drugs, with 77 percent presently utilized in one or more countries. Phytomedicines are flooding the markets of developed countries, and consumers all over the world have demonstrated a desire for natural drugs and their formulations. The emphasis is on ‘natural is better’ [3].

Today, Ayurveda has evolved into a scientific system of holistic healing that is now recognised all over the world [4].

Ayurveda is the Sanskrit word for “life science”. It is not merely a system of medicine, however, but a general philosophical technique for maintaining good health, living a long life, and treating diseases. It provides a sole blend of science and philosophy that balances the physical, emotional, mental, and spiritual components required for lasting health. This healing system believes in treating the entire person, not just the part affected by the disease. Furthermore, the emphasis is on prevention rather than cure [5].

Ayurveda evolved in tandem with religion and mythology. It can be thought of as a stream of knowledge that has been passed down from time immemorial and has been reinterpreted and brought along with it. Ayurveda is possibly the only organized science that directs ecological development, medicinal plant cultivation, and the use of specific plant parts [6].

More than 2000 drugs are listed in the “Charaka” and “Sushruta” samhitas, with 70% of them being herbal. The importance of this science will continue to grow due to its biomedical implications and place in cultural beliefs. Despite its ability to treat a wide range of diseases, medicinal plant therapy was developed in preindustrial times [6].

Besides Ayurveda, a variety of healthcare systems have been practised around the world, including Siddha, Unani, and Homeopathy, the majority of which are based primarily on herbs and diet. Globally, the early twentieth century saw a decline in the popularity of natural drugs of plant origin due to the evolution of the pharmaceutical industry (synthetic medicines), as well as a lack of interest in medicinal plant research [5].

However, the pendulum has recently dangled back, and there is a reappearance of awareness in the study and application of plant-based drugs. Natural drugs are in high demand, particularly those scientifically validated, such as Garlic, Echinacea, Ginseng *etc.* ‘Herbalism’ refers to the more recent perception of using herbs or plants in a more scientific way [7, 8]. Since the origin of civilization, plants and plant compounds have been utilized as natural drugs. They are used to care for a wide range of acute and chronic illnesses, from the common cold to complex human problems, and they're regarded as the cornerstone of indigenous drugs [9]. As per WHO opinion, approximately 80% of the worldwide population anticipates using natural products for health care owing to their fewer side effects and the high price of modern medicine [10].

As the environment becomes more polluted, life becomes more stressful, and food becomes contaminated by chemicals, there is a greater need to reconnect with nature. Although allopathy and modern medicine are unquestionably effective and necessary in certain situations, there are some pitfalls where an alternative system of medicine offers some advantages.

NEED FOR DRUGS FROM PLANT ORIGINS OVER SYNTHETIC DRUGS

Allopathic treatment entails the administration of drugs that introduce toxins into the body. The body may be unable to eliminate or cope with them, resulting in adverse effects. Herbal medicines, which are based on a traditional system of natural cure, cleanse the body, increasing its ability to heal itself and defend against invaders while causing virtually no side effects.

Allopathic treatments are incapable of providing long-term solutions. Its most prevalent strategy is to suppress both physical and mental signs and symptoms. Natural drugs treat the symptoms as an indication or evidence of a deeper

CHAPTER 5

Immunomodulators: Chemistry and Analytical Techniques

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Abstract: Immunomodulators are substances that either enhance or suppress the immunity of the host. Immunomodulators have been used for ages in Ayurvedic Medicine and Traditional Chinese Medicine. In the surge of modern medicine, many chemically derived substances are used as immunomodulators. Historically, plants present a rich source of these therapeutic agents. Researchers have used these lead structures for exploring the underlying mechanisms of immunomodulation so that newer, safer agents can be designed and used clinically. Microbial sources have also been tried in search of immunomodulators. Chemically, these are a diverse group of substances that act on varied signaling pathways to cause immunomodulation. The involvement of the immune system in many diseases and disorders makes these agents essential in the treatment of these diseases, *e.g*., cancer. This chapter discusses the chemistry of a selected few commonly known plant-derived immunomodulators along with their biological evaluation methods and provides a broad overview of their therapeutic potential with particular emphasis on the mechanism of immunomodulation.

Keywords: Adaptive Immunity, Cytokines, Emodin, Immune checkpoint inhibitors, Immunomodulators, Innate Immunity, Interleukins, Quercetin.

INTRODUCTION

Innate immunity is the first line of defense that is present in almost all vertebrates and even in the multicellular organisms; its main role being recognition of the foreign invaders such as pathogens. In most cases, the innate immune system recognizes a particular region of the pathogen known as Pathogen Associated Molecular Patterns (PAMPs) employing the so-called Pathogen Associated Receptors (PARs). The other arm of the immune system, *i.e*., adaptive immunity,

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involves the generation of B and T cell receptors somatically during the B and T cell development and so are not passed on to the next generation. Hence antigenic determination cannot be made by them until they are being made to recognize them [1]. In other words, the innate immune system is more general in its capability to identify the antigens, whereas the adaptive immune system is more specific in this aspect.

The innate immune system comprises of cells such as mast cells, basophils, natural killer (NK) cells, macrophages, eosinophils, neutrophils, and dendritic cells. These cells have their way of killing and eliminating the pathogens, some of which include releasing histamines, cytokines, or chemokines, or making the cells follow the apoptotic (programmed cell death) path, by phagocytosis, or presenting the antigens to T cells. The adaptive immune system comprises of B cells, CD4+, and CD8+ cells. The B cells eliminate the pathogen mostly by the humoral immune response or by producing antibodies. The CD8+ cells recognize most of the cancerous and virus-infected cells (intracellular pathogens) and make them undergo apoptotic pathways. The CD4+ cells, which constitute Th1, Th2, Th17, and regulatory T (Treg) cells, are involved in the production of cytokines such as Interferon γ (IFN-γ), Interleukin-2 (IL-2), IL-4, IL-5, IL-13 and IL-17 [2].

The immune system is capable of recognizing self (own body cells, proteins), from non-self (antigen), which could be anything such as the viral coat, bacterial lipopolysaccharides, viral genetic material, or any substance which does not belong to the host. The problem arises if the immune system does not recognize particular antigens resulting in a particular disease (or pathological condition) or if it recognizes its own body cells that result in auto-immune disease or disorder. The latter is mostly because of the adaptive immune response since the antigen-binding site is a result of a random genetic mechanism [1]. The role of immunomodulators is essential in these cases, which helps to maintain the homeostasis of the immune system. The present chapter thoroughly discusses the chemistry of various immunomodulators derived from natural sources, followed by the analytical techniques and finally, the efficacy of immune modulation demonstrated by some of the plant-derived immunomodulators.

IMMUNOMODULATORS

Precisely, immunomodulators are substances that help to maintain the homeostasis of the immune system, *i.e*., it could be either immunosuppressant or immunostimulant or immunoadjuvant. These agents are administered to maintain the balanced functioning of the immune system. The immunosuppressants are agents that aid in suppressing the immune system. The suppressed immune function is desirable in patients suffering from auto-immune diseases such as

rheumatoid arthritis (RA), Systemic lupus erythematosus (SLE), or for suppressing the immune response in patients who have undergone organ transplant surgery to prevent graft rejection [2]. On the other hand, the immunostimulants are agents which enhance or boost the immunity of the host. Immunostimulants are mostly indicated for providing resistance to some diseases, leading to enhanced immunity without the use of vaccines [3], *e.g.*, various Immunostimulants prescribed during the COVID-19 pandemic. The immunoadjuvants are those substances which are used in a vaccine along with the antigens as carrier material. The antigen itself, in this case, would be very small and hence will not be recognizable by the host immune response. So, immunoadjuvants are used, which aid in better recognition by the immune system, leading to the profuse response by the immune system and hence, improved protection [4]. Both the Immunostimulants and immunomodulators may work *via* specific pathways or non-specifically. With respect to chemotypes, the immunomodulators could be small-molecules, proteins or peptides, carbohydrates, nucleic acids, or lipids [5]. While the field of immunomodulators is so very vast, no attempt is made to discuss all the types of immunomodulators but small-molecules, particularly those obtained from natural sources.

Commercially, many immunosuppressants are available, some of which include Rapamycin (**1**), Sirolimus, Fig. (**1**) Cyclosporin A (**2**), Cyclophosphamide (**3**), Azathioprine (**4**), and Cinanserine (**5**). Rapamycin, a macrocyclic compound produced by *Streptomyces hygroscopicus,* disrupts the T-cell growth-promoting cytokines like IL-2 or IL-4 and acts as an anti-proliferative agent. It blocks the cell cycle during the mid-to-late G1 phase, thereby arresting the G/S transition [6]. Cyclosporin A inhibits the action of calcineurin, which in turn blocks the movement of cytosolic components of the Nuclear Factor of Activated T-cell (NF-AT). Cyclophosphamide is the most widely used alkylating agent, which inhibits both the adaptive and innate immune responses. Azathioprine is an immunosuppressant that is generally used in kidney transplants, and Cinanserine is an antagonist of serotonin, which suppresses the antibodies circulating in the human body [3].

The synthetic drugs, though efficacious, come with debilitating adverse effects, including toxicity such as nephrotoxicity, neurotoxicity, and gastrointestinal toxicity, among others. Also, they act upon actively growing cells such as bone marrow cells which ultimately end up in leucopenia and thrombocytopenia [3]. Compared to synthetic drugs, natural products offer several advantages [7] due to the synergistic actions of complex molecules when used in the form of an extract or preparation. At times, pure natural products offer distinct pharmacological and therapeutic activities. The successful use of natural products as sources of new drugs has created enough research interest in the global scientific community [8].

CHAPTER 6

Bioassays and Other Methods for Immunomodulators in Preclinical and Clinical Setting

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Abstract: The availability of appropriate animal models is essential for effective translation of immunomodulatory research into clinical settings. Bioassays and other methods for immunomodulators in the preclinical and clinical setting are being used to assess the quality and quantification of the immune response, find the best suitable route of administration and formulation method, protect the transmission of infection, and assess the safety and toxicity of immunomodulators. Identifying the appropriate animal model has become very important, since each model has its own pro's and cons. The scope of this chapter is to outline the assaying of immunomodulatory activity, the approaches and the experimental strategies. This chapter discusses various *in-vitro* models such as cell lines, assays and murine models, which are being used for quantification of the immune response, assessment of overall immune functions, immunosuppressive activity, screening of anti-allergic drugs and agents used in the treatment of various autoimmune disorders and transplant-related and autoimmune diseases. The most important questions that we should keep in mind while choosing a suitable animal model are, selection of suitable species, physiological relevance of model, immunological functions to be evaluated, and its practical implications.

Keywords: Adaptive Immunity, Immune System, Immunomodulation, Innate Immunity.

INTRODUCTION

Scientist Edward Jenner, who performed the first 'vaccination' against smallpox in 1796, brought the concept of Immunomodulation. Further, various efforts were undertaken to modify the immune system to combat both external and internal pathogen attacks, with the intention of improving disease resistance. With this

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goal, the immune response can be modified by applying immunosuppression, immunestimulation, and immunerestoration [1 - 3]. Immuno-stimulatory adjuvants are required in vaccines to activate the innate immune system and generate specific adaptive immunological responses. Immunoadjuvants increase the amount of antibody generated while decreasing the amount of antigen required for injection and, as a result, the frequency of injection. Examples of best-known types of immunoadjuvants are Toll-like receptor agonists (TLR), inorganic immunoadjuvants, plant-derived immunoadjuvants, exosomes, and endogenous proteins. However, their short response rates and undesirable effects limit their use. As a result, there is a continued demand for immunoadjuvants with enhanced efficacy and lower toxicity, as well as improved bioactivity and bioavailability [4, 5]. Also, many novel multifunctional adjuvants are being developed with the modified delivery system. Nanoparticle-based immunoadjuvant [4] and the incorporation of multifunctional immunoadjuvants into pDNA/mRNA vaccines [6] are two of the most promising. Immunostimulants are appealing compounds that trigger the immune system for disease prevention and improve natural resistance to numerous viral and bacterial infections. Immunostimulants act in specific and non-specific ways in the body, causing the production of specific antibodies and cytokines, which can be used to treat infectious disorders and diseases with suppressed immunity like malignancies, AIDS, SARS, *etc* [7, 8]. Immunosuppressive drugs are used to treat severe hypersensitivity immune reactions, transplant-related and autoimmune diseases caused by autoreactive B lymphocytes or T lymphocytes (CD4+ or CD8+ cells) [9, 10].

ASSOCIATION OF INNATE IMMUNITY AND ADAPTIVE IMMUNITY AND THEIR MEASUREMENTS

Innate immunity is the first-line immune system with no memory generates fast and blunt, non-specific responses to infection and tissue injury in response to the signals from germline-coded proteins termed Pattern Recognition Receptors (PRRs). PRRs have evolved to recognize molecular patterns shared by numerous pathogen classes called Pathogen-Associated Molecular Patterns (PAMPs) or Damage-Associated Molecular Patterns (DAMPs). To activate the adaptive immune system, dendritic cells, macrophages, mast cells, neutrophils, basophils and eosinophils directly interact with other cells or release cytokines and other compounds such as reactive oxygen species, nitric oxide, and lipid inflammatory mediators which are involved in the inflammatory response. Other lymphocytes without antigen specificity, such as gamma-delta T cells and Natural Killer (NK) cells, are considered innate cells with some resemblance to effector lymphocytes [11, 12]. Dendritic cells (DC) are important agents between innate and adaptive immunity by triggering primary immune responses. DC, as a component of the in-

nate immune system, organises and transports information from the outside world to the adaptive immune system [13].

Adaptive immunity generates an antigen-specific, flexible response and has immunologic memory. So, it permits vertebrates to thrive in an environment where they are constantly exposed to infections. This system relies on the clonal selection and expansion of lymphocytes *via* antigen (T cell and B cell) receptors. Antigen receptors are clonal receptors that have been genetically altered to bind to antigens expressed in Major Histocompatibility Complex (MHC) molecules on antigen-presenting cells [14].

Although the innate and adaptive immune systems are opposite, independent systems of the host response, they work together see Fig. (**1**). The innate system acts as the first line of defense against pathogens, thus activating antigen-specific cells. These antigen-specific cells further help in recognizing and responding to microorganisms. As a result, coordination between innate and adaptive immune responses is important, even though they operate *via* different mechanisms.

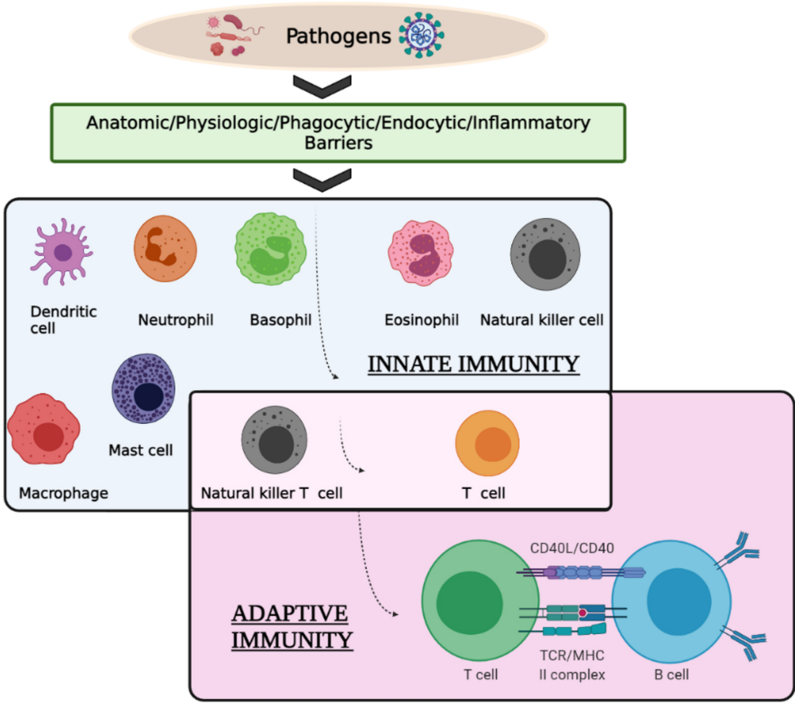

Fig. (1). Association between innate immunity and adaptive immunity.

CHAPTER 7

Natural Immunomodulators in Cancer Therapy

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Abstract: Cancer is a complex disease, ranking among the top causes of mortality worldwide. There are numerous therapies available however, they are showing limited success in a complete cure. The advanced treatment regime includes immunotherapy that improves the body's natural defences. The approved immunotherapies are imiquimod (Zyclara®), lenalidomide (Revlimid®) pomalidomide (Pomalyst®), and thalidomide (Thalomid®). However, these therapies have severe side effects like nausea, high blood pressure, blood clot, severe allergies, *etc.* Hence, natural products with immunomodulatory properties are being widely used as adjuvant therapy in cancer treatment. Plant secondary metabolites, such as curcumin, resveratrol, zerumbone, quercetin, genistein and betulinic acid, which are used as a member of the cancer medications and possess immunomodulatory potential, have been described in this chapter. We have discussed the mode of action, *in vitro*, *in vivo*, formulation studies and plant source of these natural immunomodulators. This chapter also discusses the current state of these pure compounds in context to their development as anticancer treatments in the future.

Keywords: Anticancer, Antitumor, Curcumin, Cytotoxicity, Immunotherapy, Natural Immunomodulators, Quercetin and Betulinic Acid, Resveratrol.

INTRODUCTION

Cancer imposes the largest worldwide healthcare burden as it is the second prominent cause of death globally, accounting for approximately 9.6 million deaths in 2018 [1 - 3]. At present, chemotherapy, endocrine treatment, targeted cure, radiation, surgery and immunomodulation are used for the management of cancer [4]. Multiple genetic and epigenetic factors influence cancer cell sensitivity leading to drug resistance in cancer which has posed a huge challenge in cancer therapeutics [5]. High doses of a drug, rapid metabolism, higher elimination rate, lower bioavailability, adverse effects, and toxicity to normal cells are the drawbacks associated with the existing chemotherapeutics [6]. There are numero-

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us adverse effects of radiation therapy as well like cardiovascular disease, dermatitis, pneumonitis, and sexual dysfunction [7]. Immunotherapy is a clinically validated emerging treatment for the management of broad cancer types [8]. Tumour's immune resistance mechanisms, such as specific immune responses mediating collateral tissue damage and immune-inhibitory pathways, can be effectively targeted against cancer [9].

The immunomodulatory checkpoints like cytotoxic T lymphocyte antigen 4, CD25+ (Interleukin-2 receptor alpha chain), CD4+ (cluster of differentiation 4), foxp3-expressing Tregs (suppressor T Cells), Interleukin-2 (IL-2) and Interleukin-15 (IL-15) are used as tools to enhance the effects of immunotherapeutic. Inhibiting pro-inflammatory cytokines like Interleukin-6 (IL-6), which activate the signal transducer and activator of transcription 3 (STAT3) and NF-κβ (nuclear factor kappa light chain enhancer of activated B cells) pathways, prevents the upregulation of anti-apoptotic peptides like Bcl-2 (B-cell lymphoma 2) [10, 11]. Macrophages infiltrating the tumour microenvironment prompt the immune response to counter the tumour by increasing reactive nitrogen and reactive oxygen species, leading to DNA impairment and tumour destruction [12]. Monoclonal antibodies in unmodified form or modified with add-on toxins and radionuclides are extensively used as magic bullets to treat cancer as an immunotherapeutic [13]. However, these monoclonal antibodies have limitations in cost, production and purification, risk of virus association, *etc* [14]. Currently, lenalidomide (Revlimid®), pomalidomide (Pomalyst®), Imiquimod (Zyclara®), and thalidomide (Thalomid®) are among the authorised immunotherapies against cancer. Lenalidomide and pomalidomide are the synthetic analogues of thalidomide used against several haematological malignancies and regulates various aspects of the immune system, including cytokine production, T cell co-stimulatory activity, and Natural Killer cell cytotoxicity [15, 16]. However, these therapies have severe side effects like severe allergies, nausea, high blood pressure and blood clot [17].

For ages, nature-based treatment systems, such as Ayurveda, Unani, Siddha, and Traditional Chinese Medicine have used immunomodulation for healing [18, 19]. Several plants like *Withania somnifera*, *Paris polyphylla*, *Astragalus melanophrurius*, *Astragalus oleifolius*, *Ocimum sanctum*, *Panax ginseng*, *Alternanthera tenella*, *Terminalia arjuna*, *Tinospora cordifolia*, *etc.* have been used as immunomodulatory agents [20]. These plants, in the form of various ayurvedic formulations such as Rasayanas, are known to inhibit tumour development in mice by improving natural killer (NK) cell activity while enhancing the production of Granulocyte-macrophage colony-stimulating factor (GM-CSF), Interferon gamma (INF-γ), and IL-2 [19]. A formulation of *Withania somnifera* containing a 1:1 ratio of alcoholic extract of roots and leaves showed

enhanced Type 1 T helper (Th1) expression in tumour-bearing mice, repressing the expression of STAT3. This formulation has also shown increased (cluster of differentiation 8) CD8+ and CD4+ T cell proliferation which is useful in inhibiting cancer growth [21]. Numerous *in-vitro* (human lung cancer cell lines- A549, H1264, H1299, Calu-6) and *in-vivo* studies of *Panax ginseng* against lung cancer have been reported indicating its multiple molecular targets of immunomodulation [22]. A nano-particle of *Panax ginseng* using silver has shown cytotoxicity against the A549 cell line (IC_{50} value 20 µg/mL) by inducing apoptosis *via* the p38 mitogen-activated protein kinase (MAPK)/p53 pathway [23].

These studies indicate that plant secondary metabolites have the potential to modulate the immune system through multitargeted pathways and produce the desired pharmacological action, which is also applicable to treating cancer. This hypothesis has been proved for a few Natural Products such as curcumin, resveratrol, quercetin, genistein, betulinic acid, and zerumbone Fig (**1**). [24]. This chapter examines numerous secondary metabolites showing anti-cancer activities through immunomodulation Table **1**, and the established natural products have been described to the greatest extent possible.

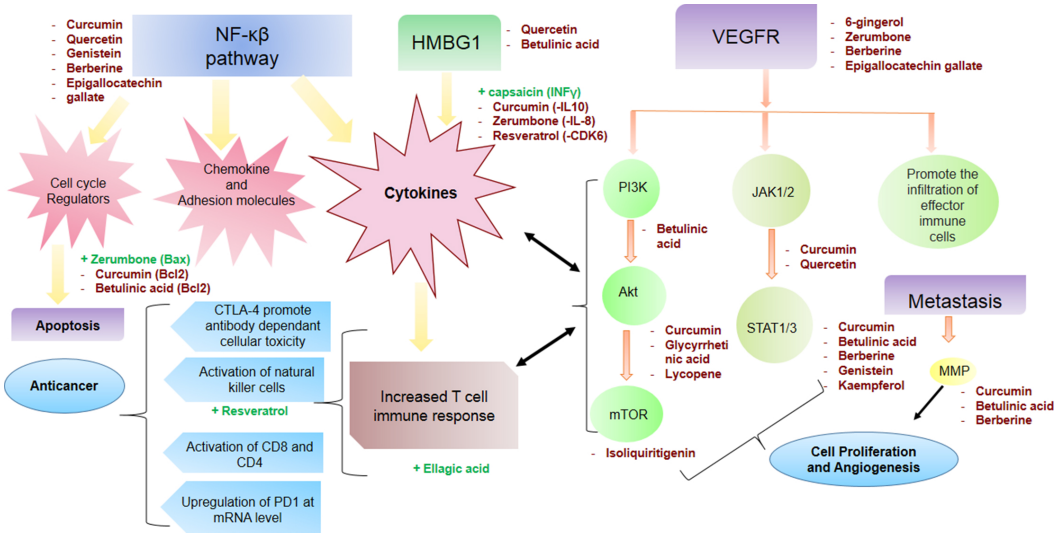

Fig. (1). Anticancer activity of selected natural products *via* immunomodulation (-ve sign indicates inhibition and +ve sign indicates activation).

CHAPTER 8

Natural Immunomodulators for Infections and Other Diseases

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Abstract: Infection is one of the most common occurring issues in an individual. Diseases caused by infections hamper the immune system of an individual. To modulate the immune system, immunomodulatory drugs work by either stimulating or suppressing the immune system. Several drugs like levamisole and azathioprine are available in the market today to overcome various infections. But an alternative is required to overcome the drug resistance and other side effects associated with these available drugs. To tackle these problems, many plant-based immunomodulators are being explored and have proven to be beneficial against these infections. This chapter focuses on the mechanism of action and application of natural immunomodulators like Curcumin, Resveratrol, and Genistein on various infections. The primary goal of this chapter is to understand the role of natural immunomodulators in the body for various infections and related disease conditions. With the help of findings, one can conclude that all-natural immunomodulators have areas that need attention, including their therapeutic risk-benefit ratio and their target binding affinity for various infections. However, further investigations into these drugs are necessary for a clear understanding to maximize their clinical applications

Keywords: Natural Immunomodulators, Antimicrobial, Antibacterial, Antiviral, Antiparasitic, Ayurveda, Curcumin, Genistein, Immunosuppressants, Immunostimulants, Infection, Resveratrol.

INTRODUCTION

An immune response is the ability of the human body to be shielded, protecting itself against various harmful agents [1]. Immunomodulators are drugs that modify the response of the immune system either by stimulating or suppressing

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the release and production of antibodies in human serum. They are used to restore the level of the immune response [2]. A well-balanced immune system enhances defence mechanisms against various infections, hypersensitivity reactions, and autoimmune diseases. Immunomodulators are used in treating chronic infections, cancer, and organ transplantation [3]. There is a rise in the emergence of novel immunomodulators as the understanding of autoimmune diseases increases globally [4, 5]. Immunostimulants act by showing prophylactic action in normal individuals by activating the primary immune responses [6]. These agents are used in the treatment of inflammation and cancer by enhancing the body's defence mechanism. T and B lymphocytes act as primary targets for immune-stimulating agents. Immunostimulants act by affecting cytokines and specifically inhibiting or enhancing populations of immune cells like lymphocytes, neutrophils, macrophages, NK cells, and cytotoxic T lymphocytes [7].

Immunosuppression mainly decreases the body's resistance to fight against infections [8]. These agents have been clinically used to treat graft rejections and autoimmune diseases and hence are termed antirejection agents [9]. They are the most widely used drug in the treatment of inflammatory bowel disease (IBD) like Crohn's disease [3]. Drugs such as prasterone and hydroxychloroquine are immunomodulators, used to manage immunological conditions like rheumatoid arthritis and systemic lupus erythematosus [10]. The present immunomodulant therapy consists of drugs that have a specific mode of action and give rise to various side effects. Some of the side effects caused by these immunomodulators are pulmonary toxicity, myelosuppression, and hypertension [11]. These adverse effects can often lead to being the cause of death in immunocompromised patients [12]. Cyclosporine is an immunosuppressant that causes adverse effects like hyperkalemia, convulsion and hepatitis when given orally or intravenously. It is not recommended during pregnancy. Other alternatives like tacrolimus and mycophenolate are used instead of cyclosporine, however, they increase the risk of diabetes [13 - 15]. Immunomodulators also manifest oral adverse effects like Sjogren's syndrome and oral lichen planus [16 - 18]. Immunostimulants are a class of immunomodulators that enhance body’s resistance against infections, while immunosuppressants are agents that inhibit or suppress the active immune system. Natural immunomodulators have the potential to fight off infections caused by microorganisms like bacteria, viruses, and fungi.

INFECTIOUS DISEASES

Infection is a bodily condition produced by the introduction of one or multiple pathogens like bacteria, fungi, and viruses. The severity of infection can range from mild to severe and sometimes may be fatal. There are four major agents

responsible for infections: Bacteria, fungi, viruses, and parasites, as depicted in Table **1**.

Table 1. Various infectious agents and diseases caused by them.

Sr. No.	Type of Infective Agent	Name	Disease	Reference
1	Bacteria	*Bacillus anthracis*	Anthrax	[19]
2	Bacteria	*Mycobacterium tuberculosis*	Tuberculosis	[20]
3	Bacteria	*Vibrio cholerae*	Cholera	[21]
4	Fungi	*Pneumocystis*	Pneumonia	[22]
5	Fungi	*Candida species*	Mucocutaneous infections	[23]
6	Virus	*Human immunodeficiency virus*	Acquired Immuno Deficiency Syndrome (AIDS)	[24]
7	Virus	*Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus*	Covid-19	[25]
8	Virus	*Poliovirus*	Poliomyelitis	[26]
9	Virus	*Hepatitis virus*	Hepatitis	[27]
10	Parasite	*Plasmodium species*	Malaria	[28]
12	Parasite	*Wuchereria bancrofti*	Filariasis	[29]

Antibiotics are active drugs that are used to treat various infections. Antibiotics either destroy or prevent the multiplication of microbes, which allows the immune system to clear infections. Antibiotic resistance, these days, is limiting the efficacy of many of these drugs. Using an antibiotic is advised even after no more symptoms are seen to heal the infection and prevent the growth of resistant microbes. Antibiotic development presently focuses on targets that are critical for bacterial metabolism; however, studies into how bacterial species communicate with one another could lead to the creation of newer medications that reduce resistance. Antibiotics are not effective against infectious diseases caused by viruses like influenza; instead, antiviral drugs are used for viral infections. These drugs elicit their therapeutic effect either by limiting or hampering the multiplication capacity of the virus or by increasing the immunological response of the body to the infection. Antiviral drugs are divided into various categories, each of these is used to treat different types of viral infections, including influenza, HIV, herpes, and hepatitis B. Viruses, similar to bacteria, evolve throughout time and become resistant to antiviral medications [30]. Several studies have looked at the current state of immunomodulatory techniques for infection prevention in neonatal immunological deficiencies and recent

CHAPTER 9

Delivery of Immunomodulators: Challenges and Novel Approaches

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Abstract: Immunomodulators can be either synthetic in origin or naturally obtained. Natural plant-based compounds can influence the immune system by either affecting antibody secretion to control the infection or affecting the functions of immune cells, thus contributing to maintaining immune homeostasis. Phytochemicals in plants, such as polysaccharides, lactones, flavonoids, alkaloids, diterpenoids and glycosides, have been reported to possess immunomodulating properties. However, there are many challenges limiting the clinical use of natural immunomodulators. In this chapter, we have discussed in detail standardization, formulation development, route of administration and regulatory concerns of natural immunomodulators. In order to overcome these challenges and ensure that natural immunomodulators reach the target site at therapeutic concentrations, different polymer and lipid-based nanocarrier delivery systems have been developed. These nanocarriers by virtue of their size, can easily penetrate and reach the target site and deliver the drugs. Many nanocarriers like liposomes, niosomes, nanoparticles, microemulsions, phytosomes and other vesicular systems designed for natural immunomodulators are discussed in this chapter.

Keywords: Drug Delivery Challenges, Drug Delivery Systems, Immunomodulators, Immunostimulants, Immunosuppressants, Immunoadjuvants, Nanocarriers, Natural Products, Phytoconstituents.

INTRODUCTION

Immunity is the ability of the body to combat a wide array of potential pathogens, resist diseases and prevent any organ or tissue damage. It comprises of series of balanced complex, multicellular and physiologic mechanisms that enable the host body to differentiate between self and foreign entity and eliminate it [1, 2]. Vertebrates have an extremely complex and advanced immune system, which is capable of producing a large variety of cells to arrest the growth of various microbes and the development of subsequent infections. The immune system is

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not confined to any particular organ or tissue; rather, it is active for the entire body of the host. The immune system is simply a collaborative amalgamation between cells and proteins that work systemically to provide protection against infection or any foreign entity [3].

The development process of all immune cells originates from hemopoietic stem cells in the bone marrow. These cells either migrate to the thymus and differentiate into mature T-lymphocytes (T-cells) or remain in the bone marrow to differentiate and mature into B- lymphocytes (B-cells). B-cells differentiate into plasma cells, eventually producing immunoglobulins or antibodies. In a mature state, B-cells are generally found in bone marrow, spleen, intestine, lymph nodes and bloodstream. On interaction with a foreign entity or an antigen, B-cells mature into plasma cells and produce highly specialized serum protein molecules to destroy antigens; B-cells also mature as memory cells to ensure a quick response to the same antigen if the infection is encountered again. After leaving the thymus, T-cells populate either in the spleen, bone marrow, lymph nodes or blood and further mature into cytotoxic T-cells and helper T-cells for exhibiting cell-mediated immune response. T-cells have antigen-specific molecules that help them recognize and eliminate specific antigens. Helper T cells assist B-cells to produce antibodies and assist killer T-cells in their attack on foreign entities [4].

Immunity is categorized as active immunity and passive immunity. When immunity is achieved by exposure to a disease organism triggering the host immune system, it is an active type of immunity. This type of immunity is long-lasting and involves memory B-cells. Natural active immunity is achieved when the body is exposed to an infection or by introducing killed or attenuated forms of the disease pathogens through vaccination, called induced active immunity. Passive immunity is acquired when antibodies are directly provided to an individual without involvement or activation of the immune system. Natural passive immunity is attained from the mother to her child by the passage of antibodies either through the placenta or through breast milk. Passive immunity is transient in nature and lasts only for a few weeks to months but provides immediate protection in contrast to active immunity, which develops after a longer period of time, however, it is long-lasting [5, 6].

Over the past few decades, the health industry and biomedical research have collectively emphasized the importance and maintenance of the healthy immune system for prevention against various infections and rapid recovery from diseases. Ironically, immunity is not always as beneficial to the host body, especially when it causes tissue damage, hypersensitivity and or leads to other autoimmune diseases. In such cases, it becomes necessary to modulate immunity by suppressing it in order to treat autoimmune diseases or prevent graft rejection. On

the other hand, in infectious and by enhancing immunity to fight off infections. Over the years, research has led to the development of a group of molecules that can target the immune system [7, 8].

NATURAL IMMUNOMODULATORS

Synthetic and chemical immunomodulating drugs have been used to treat cancer, graft rejections and other autoimmune disorders for years. For example, cyclophosphamide is a widely used alkylating agent that acts as an immunosuppressor against animal and human malignancies. It has the tendency to inhibit both humoral and cell-mediated immune responses. Cyclophosphamide, however, is associated with renal toxicity and renal failure. Synthetic immunomodulators are often associated with nephrotoxicity, hypertension, hepatotoxicity, hirsutism, gastrointestinal toxicity (nausea, vomiting, diarrhea, anorexia and abdominal pain), neurotoxicities such as headache, insomnia, pain, cardiovascular toxicity and metabolic toxicity like hyperkalemia, hypomagnesemia, hyperglycemia *etc.* Drugs like azathioprine used as a disease-modifying anti-rheumatic drug (DMARD) also affect rapidly growing cells, including bone marrow and gastrointestinal cells resulting in thrombocytopenia, leucopenia and gastrointestinal toxicity. Anti-thymocyte globulin, synthetically prepared polyclonal IgG component from the serum of various animals used in the treatment of renal allograft rejection causes serum sickness and nephritis. Some of the chemical immunomodulators also cause fever, leucopenia, thrombocytopenia, skin rashes and infertility due to the destruction of testicular and ovarian cells [9].

Clinical drawbacks and limitations of synthetic immunomodulators have led to increased interest in the study of natural and plant-based immunomodulators. Studies have indicated that many natural products have the ability to repair impaired immune systems either by activating the components of innate immunity, such as stimulation of macrophages and lymphocytes, or by modulating the cytokine profile and stimulating the process of apoptosis, thus reducing the incidence of infections. Natural immunomodulators can help potentiate humoral immunity (HI) or cell-mediated immunity (CMI) by causing a significant increase in serum immunoglobulin (Ig) levels and other mediators of CMI in various body fluids. Natural products also cause a significant increase in the populations of mature T cells, interleukins, tumor necrosis factor-alpha (TNF-α), interferons, *etc.* Natural immunostimulants can also activate humoral as well as cell-mediated immune response against tumors facilitating recognition and destruction of the tumor, and enhancing the ability of the host to tolerate damage caused by toxic chemicals [1].

CHAPTER 10

Marketing Strategy & Regulatory Perspective for Natural Immunomodulators

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Abstract: Many natural products, such as *Azardicaindica*, *Curcuma longa*, and *Ocimumsanctum*, are often used as immunomodulators. The increased prevalence of chronic diseases, along with the negative effects of synthetic immunomodulators, has resulted in the establishment of a global natural immunomodulator market. For researchers, complementary and alternative medicine provides a new target for drug discovery approaches and medication development. Ayurveda, Homeopathy, Naturopathy, and the Chinese medicine system are examples of complementary and alternative medicine approaches. Phytoconstituents with therapeutic action are included in the Complementary and Alternative Medicine (CAM) categories of natural goods. In Europe, natural immunomodulators are considered food supplements, while in the United States, they are utilized as dietary supplements. In India, it is controlled by the Ministry of AYUSH (Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homeopathy). With the help of the literature findings, we understand that even natural phytoconstituents also require and must undergo well-defined regulatory approval processes to launch in the market. But the regulation slightly differs as per the country and region. With the help of all the findings, one can conclude that the regulation of natural immunomodulators is equally important to set its marketing strategies as well as for its post-marketing surveillance as compared to the synthetic molecules. With this objective, the primary goal of this chapter is to draw more attention to the regulatory aspects of natural immunomodulators by comprehending the information on natural immunomodulator marketing strategy as well as the legislation that governs it.

Keywords: Guidelines, Legislation, Marketing Strategies, Natural Immunomodulators, Regulatory Agencies.

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INTRODUCTION

Immunomodulators can help combat and mitigate diseases and illnesses caused by immunodeficiencies [1 - 6]. Several metabolites that decrease immune responses may be effective in the treatment of autoimmune illnesses [7, 8]. Reactivation of latent Tuberculosis (TB) is another documented unfavorable effect, particularly in association with new-generation immunomodulatory medicines [9, 10].

Pharmaceutical drug laws, commonly called pharmaceuticals regulatory guidelines, are a collection of authorized, procedural, and technical requirements used by government agencies to guarantee patient safety, drug efficacy, and purity, as well as the reliability of the product. The word "regulation" encompasses comprehensive elements (for example, rules, recommendations, processes and policies) with varied legal bases and jurisdictions [3, 4]. This is achieved by a variety of regulatory processes performed throughout the life cycle of drug discovery and development, which includes premarket screening and analysis of new medicines, an inspection of manufacturing facilities, legislation, marketing, and post-market surveillance. Each country has unique rules that govern invention, production, screening, advertising, and post-marketing research. The goal is to keep drug standards high at all times to meet the needs of health maintenance of each country [5].

In India, the regulatory bodies are the Central Drug Standard Control Organization (CDSCO), the Indian Council of Medical Research (ICMR), and the Ministry of Health and Family Welfare (MoHFW). The CDSCO is responsible for carrying out the tasks delegated by the Central Government under the jurisdiction of the Drugs and Cosmetics Act. It is responsible for guaranteeing the quality, usefulness, and purity of medications distributed to the public at both the federal and state levels. CDSCO is in charge of drug importation, new drug authorization, clinical trials, and meetings of the Drugs Technical Advisory Board (DTAB) and Drugs Consultative Committee (DCC). The CDSCO plays a key role in approving specific licenses through the Central Licensing Approval Committee. ICMR is considered one of the oldest clinical study organizations in the world and the best framework in India to design, coordinate, and promote biomedical studies. The organization is supported by the Government of India through the Department of Health and Family Welfare [6, 7]. The Union Health Minister is in charge of the governing body. The Scientific Advisory Board comprising notable professionals in the field of life sciences and biomedical areas, advises the CDSCO on technical and scientific concerns [8, 9].

The US Department of Health and Human Services (HHS) is the primary organization in charge of preserving the health of all Americans and providing

basic humanitarian assistance. HHS has 11 operational departments, including eight US public health services agencies and three human services agencies. These departments offer a wide range of health and human services, as well as life-saving scientific studies. The Food and Drug Administration (FDA) is among 11 agencies within the Department of Health and Human Services responsible for ensuring that the product is healthy and genuine. FDA authenticates the quality and confirms that animal and human medicament, biopharmaceuticals, and surgical instruments are medically beneficial, and computerized devices emitting radiation are harmless. The FDA is divided into five offices that handle various functions: Medical Products and Tobacco, Foods and Veterinary Medicine, Global Regulatory Operations and Policy, Operations and Policy, and Planning, Legislation, and Analysis.

The Centre for Drug Evaluation and Research (CDER) is a department of the Division of Medical Products that regulates biological therapeutics and generic pharmaceuticals. The CDER plays an important role in public health by ensuring that safe and effective medications available to help people in the United States live healthier lives. CDER regulates over-the-counter and prescription pharmaceuticals, including biological therapies and generic drugs, as part of the US Food and Drug Administration (FDA). CDER The Center for Drug Evaluation and Research has twelve separate offices. There are several types of the department, each of which has its subsection. To sell medicinal products or drugs in the United States, pharmaceutical companies must first obtain the product cleared by the US FDA. Each product must go through a rigorous certification process established by the Centre for Drug Evaluation and Research to receive approval [10, 11].

Apart from India and America, “The Pharmaceutical and Food Safety Bureau” (PFSB) of the Ministry of Health, Labour, and Welfare (MHLW) is the pharmaceutical regulating authority of Japan. The Pharmaceuticals and Medical Devices Evaluation Center (PMDEC) is the decision body concerned with new drug approvals [12, 20]. The Organization for Pharmaceutical Safety and Research (OPSR), often known as “KIKO or “the DO” (Drug Organization), is an independent entity affiliated with MHLW, responsible for negotiating drug development projects with companies. The GCP (Good Clinical Practice) guideline will improve the ethical and scientific quality of studies conducted in Japan. It may also improve relationships between medical professionals and patients if the requirement for explicit informed consent in clinical trials leads to the provision of a comparable level of patient information in routine care and changes physicians' traditional paternalistic attitude toward patients. The GCP guideline was implemented in Japan in 1997. International Council for Harmonization-Efficacy guidelines (ICH-E6), sometimes known as “the new

CHAPTER 11

Natural *vs*. Synthetic Immunomodulators

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Abstract: Immunomodulators are key components in deciding immunity status and development in an individual. The topic has been under more emphasis, especially during and after the COVID-19 pandemic phase. Several plants with medicinal potentials are appreciated in traditional medicines for their healing perspective and have been technically examined for their immunomodulation potential. A number of plant-based bioactive compounds have been extracted and purified with such bioactivities that can rationalise their usage in conventional medication in the past and can stimulate further research in the future as well. Synthetic immunomodulators are significant for generating remedial or prophylactic formulations with defined chemical ingredients from regulatory perspectives. The review highlights the key immunomodulators, both synthetic and natural, until 2020. It also emphasises on market potential and commercial aspects of these. We have explained and listed several plants and their active scaffolds having immunomodulation activities along with synthetic compounds with similar bioactivity. We envisage the review to be an organised compilation and comparison of natural and synthetic immunomodulators and also focus on new chemical immunomodulator scaffolds.

Keywords: Adjuvant, Antibody-Mediated Immunity, Cell-Mediated Immunity, COVID-19, Humoral, Immunity, Immunology, Immunomodulators, Innate Immunity, Immuno-Stimulants, Plant Extracts, Synthetic Immunomodulator, Synthetic Immunomodulator, Traditional Medicine.

INTRODUCTION

The Nature of the Immune Response

In a world where we are faced with an environment that is host to innumerable microbes and toxic molecules, a functional immune system is paramount to homeostasis and good health. The environment is inhabited by commensals, parasites, toxins and various pathogens, and the pathogens continuously evolve

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with their myriad mechanisms to invade, replicate, spread, and affect the normal host functions. Phagocytic cells, like macrophages & neutrophils, cytokines, interferons, natural killer cells, and complements comprise the primary wall of our defence. These are non-specific or generalised defence mechanisms, aimed at localizing the foreign elements and eliminating them. The second wall of defence assumes some specificity. Lymphocytes and other substances such as cytokines and antibodies, and the macrophages present the antigens to two distinct types of cells: Thymus derived cells (T-cells) and Bursa derived cells (B-cells). Each lymphocyte recognizes an Immunogen. The combination of cell and antibodies-mediated immunity together accounts for combating the majority of microbes, such as fungi (both spores & mycelia), bacteria, viral particles, many parasites, cancer-induced cells, *etc.* The tertiary wall of immunity is the concerted action of innate immune responses and the products of particular acquired immunity activities.

Widely touted as the "Drugs of the 90s" immunomodulators are biological response modulators [1]. Optimum health depends on the ability of the defence mechanism to discriminate between "self (own)" and "non-self (foreign)" molecules, cells as well as tissues. The human immune response is a systematic, organized, three-layered defence mechanism comprising of both cellular and humoral immune responses.

An immunomodulator can be any substance of natural or man-made origin that can kindle, subdue, or modify the immune reaction. This includes the innate response and the adaptive reactions, too [2]. Immunosuppressants are antagonists of the immune system [3], and help prevent the rejection of implanted organs and tissues, and in controlling autoimmune disorders [4]. Many implant centers use multiple drugs, each targeted at a specific location in the T-cell activation cascade. They can generally be classified as transcription inhibitors, nucleotide synthesis inhibitors, growth factor signal inhibitors, and differentiation inhibitors. Polyclonal anti-lymphocyte antibodies, monoclonal antibodies targeted to the T-cell antigen receptor complex (OKT3, TIOB9), and monoclonal antibodies targeted to more cellular antigens, including interleukin-2 receptor alpha, which pay special attention to immune cell responses and are used as ingestion therapy and/or antidepressants, in clinical practice [5]. Immunoadjuvants are specific immune stimulants that improve immunity, especially for vaccine's efficacy [3]. They promise to be a true module for the immune response. Immunostimulants activate both innate, innate arms and flexible responses. They play a dual role depending on a person's immune system. In healthy people, they act as immunopotentiators, and in those with weak immune responses, they act as immunotherapeutic agents. Immunostimulators, in particular, are responsible for

the antigen-dependent stimulation of granulocyte and macrophages, and have a positive effect on their function [6 - 8].

NATURAL IMMUNOMODULATORS (NI)

The immune response can be altered by the host's natural resources or by external products from various sources.

Natural immunomodulators of exogenous types have been used to modulate immune response since antiquity. Traditionally, ancient Indian medicine uses plant products to modulate the immune response, as immunostimulants as well as immunosuppressors. For the past few decades, new healthcare challenges have emerged in the form of multidrug resistance of pathogens, against empirically used antibiotics. This “dark age” of antibiotics has propelled new research on immunomodulatory agents from plant, fungal, and microbial origin.This has negated the beneficial effects of the “golden era of antibiotics”. It is believed that there were ample forebodings of this situation, even before the discovery of the “Selman Waksman” antibiotics. It is disappointing to note that modern techniques in drug modelling and design have not impacted the pipeline in a massive way, as compared to the number of anti-microbial agents discovered around half a century ago. The future of combination therapy was evident much before [9].

Natural immunomodulators possess a low level of clarity in their action as compared to antibiotics. However, the current worldview is in favor of combination therapy that targets two or more specific sites in the immune system. Around 75% of the global population depends on traditional healthcare remedies. Traditional medicine relies mainly on natural sources as therapeutic and healing agents. Currently, many phytochemicals with therapeutic potential have been identified and used as immunomodulators [10].

Rasayana [10]

The word Rasayana, a combination of two words (*rasa* and *ayana*), refers to nutrition and its transportation throughout the body. Rasayana therapy enhances the qualities of rasa, enriching it with nutrients so one can attain longevity, improved memory and intelligence, freedom from disorder, youthfulness, excellence of hair, complexion and voice, optimum development of the physique and sense organs, mastery over phonetics and brilliance. As a dedicated stream of medication for immune promotion, antidegenerative and rejuvenating health care, the Rasayana therapy of Ayurveda is known to prevent the effects of ageing and improve the quality of life for healthy as well as diseased individuals. Rasayana is helpful to improve immunity and is normally advised during the degenerative phase of life, which starts from around 45 years in both males and females [10].

CHAPTER 12

Future Path and Perspectives of Immunomodulators

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Abstract: Immunity is the inherent ability of the body to fight against various infections, and foreign invaders. When the host body comes in contact with a foreign body, a series of chemical mediators are released, which collectively elicit an immune response. The biomolecules capable of stimulating, suppressing and modulating innate or acquired immunity, biological or synthetic in origin, are termed as immunomodulators or immunoaugmentors. Limited clinical use of synthetic immunomodulators has attracted the attention of researchers toward immunomodulatory characteristics of natural therapeutics. Though natural immunomodulators render their efficacy in several chronic illnesses, there are challenges that need to be addressed and resolved to make them viable alternate therapeutics. This chapter highlights the challenges and future perspectives of natural immunomodulators.

Keywords: Adaptive Immunity, Future Challenges, Innate Immunity, Immunomodulators, Novel Drug Delivery, Perspective of Immunomodulators.

INTRODUCTION

The immune system is one of the most crucial systems in the body for survival, as stated in previous chapters. It acts as a defensive system to protect the body from harmful agents and infections. It executes its service through coordinated efforts of a wide range of immune cells having specific, defined roles. The immune system discriminates between harmful and benign foreign invaders, eliminating

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them from the host system. The immune system is a complicated organ system next to the nervous system in biology.

The complexity of the immune system is observed at many levels. First, the cells of adaptive and innate immunity are interdependent and interconnected. The lymphocytes of the immune system present in a range of differentiated cell states, and they offer adaptive immunity with the help of countless cells of innate immunity.

Second, a complex network of intra- and inter-signaling pathways is operative in immune system functioning. Some of the factors that add to the complexity of the immune system are the process of immune cells education through clonal selection, cell receptors diversity, migration of cells, lymph dissemination throughout the host body, attaining immune homeostasis *via* regulating an ever-changing environment are some add to the complexity of the immune system.

Lastly, lymphocyte specificities, several recognition elements of innate immunity, depict the next level of complexity of the immune system. The feedback mechanism and regulation of immunostains is an intricate, subtle, and complex process and contributes significantly to immunity services.

THE COMPLEXITY OF INNATE AND ADAPTIVE IMMUNITY

The main four networks such as transcriptional, translation, spatiotemporal, and functional, control the overall execution of innate immunity in our body. These networks hold diverse information, including DNA sequence, RNAs, translocation information, spatiotemporal information of protein, subcellular structural details, and signaling process. Moreover, the intercellular communication networks include interactions between host and pathogen, soluble mediators like cytokines channelized linkages between a diverse pool of immune cells and other cells of tissues. The function of the immune system is quite dynamic, resulting in the non-linear behavior of several components, their interactions, feedback regulatory mechanisms, and three-dimensional positioning [1 - 4].

The major hurdles in the quantitative measurement of immune system components are complex and overlapping networks. With the advancement in analytical tools, genomics, proteomics, metabolomics, and cutting-edge technology, it would be possible to reach the depth and girth of the immune system and evaluation of natural immunomodulators. The involvement of sophisticated live and static imaging techniques with novel immunological assay warranted unraveling the complexity in the intracellular networks of the immune system.

Approaches and Challenges in Standardization of Natural Immunomodulators

Natural drugs and their phytoconstituents with potential immunomodulation activity are gaining popularity owing to new immune disorders and illnesses. In addition, complexities in the phytoconstituents have always presented challenges for the standardization of these compounds. It becomes necessary to provide sufficient preclinical data before natural medicines are subjected to clinical trials [5]. These strategies could be promising, allowing the development of new promising bioactive molecules. Within this context, an approach has been illustrated below with the studies conducted on many plant-origin drugs.

A major source of concern is the lack of consistency in pharmacological responses induced by plant extracts. This could be explained by the secondary metabolites' classic reliance on changes in the environment, which could also disrupt the repeatability of the end result with the extracts. Furthermore, the steadiness of therapeutic dose is among the main challenges that researchers face, as the amount of bioactive components generated differs due to the geographic area and ecological elements. Such issues can be resolved if the standardization principles of extracts and enriched fractions are systematically urged for all analytical studies.

The experimental investigation information recorded from immunomodulatory studies of *Phyllanthus* evidences an enthusiasm for identifying new chemical constituents from the available natural assets that can probably adapt to the immune responses of the human system. However, the challenges that are associated with the potential application of extracts of varied *Phyllanthus* species and the bioactive compounds as immunomodulators need to be examined.

The bio-active components of *Phyllanthus* species, namely phyllanthin, hypophyllanthin, ellagic acid, gallic acid, corilagin, niranthin, and geraniin, are highly variable in their expressions of quantity achieved at different elevations, which makes it challenging to retain quality in each batch.

The characterization of bioactive components responsible for the immunomodulation activity of plant extracts, as well as qualitative and quantitative evaluations of the chemical biomarkers for standardization and establishing the basic mechanisms of action, should have been the focus for future investigation into *Phyllanthus* species.

Earlier research studies have reported the contradictory effects of *Phyllanthus* extracts on immunomodulating activity. Very few studies have been performed on

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