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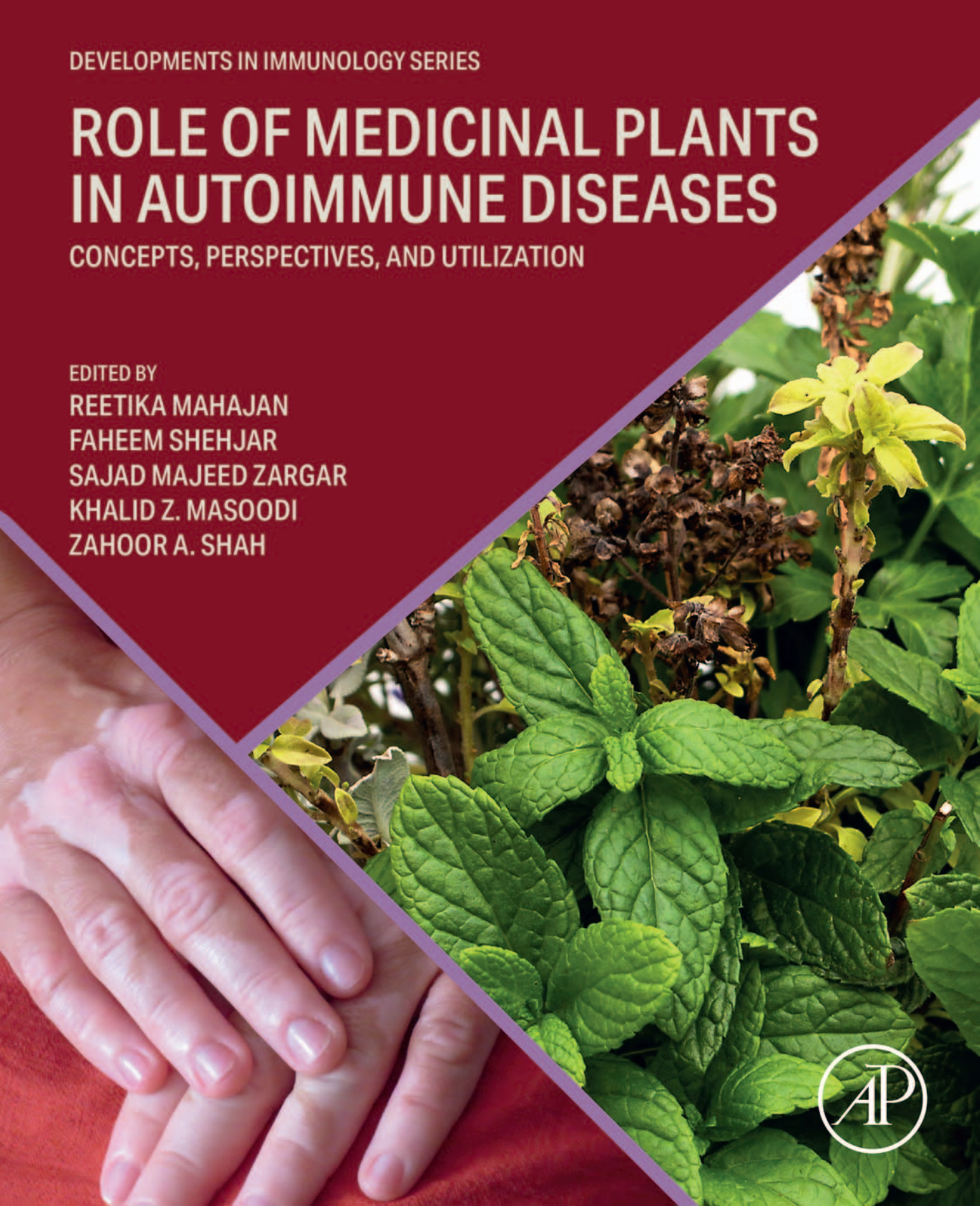

Role of Medicinal Plants in **AUTOIMMUNE DISEASES**

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Developments in Immunology

Role of Medicinal Plants in AUTOIMMUNE DISEASES

Concepts, Perspectives, and Utilization

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CHAPTER 1

Introducing immunology: Types of immunity, immune responses, deficiencies, and disorders

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1. Immunology: Coming of age

Immunology is a field of medicine focused on the immune system and its responses. The immune system is responsible for protecting the body from foreign invaders such as bacteria, viruses, cancer cells, and toxins, thereby helping to fight infections and maintain overall health (Sompayrac, 2022) The immune system's ability to resist microorganisms and maintain homeostasis is referred to as "immunity," while individuals who are deficient in immune defenses are considered immunodeficient or immunocompromized. An immunogen is a substance that causes an immune response, and the substance that reacts with the immune response and produces antibodies is called an antigen (Kozma et al., 2020).

Immunology is a relatively new branch of medical science and microbiology. It originated from the study of infectious diseases and the body's response to them. The field of immunology saw significant advancements in the late 19th century, particularly with two key discoveries. The first was the identification of phagocytic cells by Elias Metchnikoff, and the second was the discovery of antibodies by Emil Behring and Paul Ehrlich. These findings contribute to understanding adaptive and innate immunity (Kaufmann, 2019). Other notable contributors to the field of immunology include Edward Jenner, known as the "father of immunology," who developed the first effective vaccine to protect against smallpox, and Louis Pasteur, who furthered understanding of the germ theory of disease and proposed the use of vaccines for prevention and treatment (Gaynes, 2023).

Throughout the 20th century and into the present day, many scientists and researchers have made significant contributions to the study of immunology. Karl Landsteiner discovered blood groups in 1901 (Vlaar, 2022), while Gerald Edelman and Rodney Porter determined the structure of antibodies in 1959 (Yuan et al., 2023) In more recent years, Carl H. June discovered chimeric antigen receptor (CAR) T cells, which have been used in the treatment of refractory and relapsed chronic lymphocytic leukemia (Singh et al., 2020). These examples demonstrate the ongoing nature of immunological research and the continuous progress being made in the field.

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2. Innate versus adaptive immunity

Innate and adaptive immunity are the two primary defense mechanisms of the immune system (Fig. 1.1). Innate immunity is the immediate, nonspecific response that combats invading pathogens within minutes or hours without relying on immunological memory (Roy et al., 2022). It serves as the first line of defense and is not triggered by prior exposure to specific stimuli. On the other hand, adaptive immunity, which is antigen-dependent and antigen-specific, relies on immunological memory to mount a more targeted and systemic immune response upon subsequent encounters with the same antigen (Sette & Crotty, 2021). While the adaptive immune response takes longer to initiate after antigen exposure, it plays a crucial role in providing long-term protection. Any deficiencies in either of these mechanisms can lead to immunodeficiency or autoimmune disorders.

2.1 Innate immune response: PRRs, PAMPs, and cellular components

Innate immunity encompasses various types of defense, including anatomical barriers (e.g., skin and mucous membranes), physiological barriers (e.g., temperature and low pH), endocytic and phagocytic processes, and inflammation (Diamond & Kanneganti, 2022). Pattern recognition receptors (PRRs) are integral to innate immunity as they recognize specific molecular structures present on pathogen surfaces, damaged cells, or apoptotic host cells. PRRs play a crucial role in providing immune protection against infections and tumors by initiating specific immune responses (Li & Wu, 2021). They enable immune cells to differentiate between pathogens with similar characteristics and

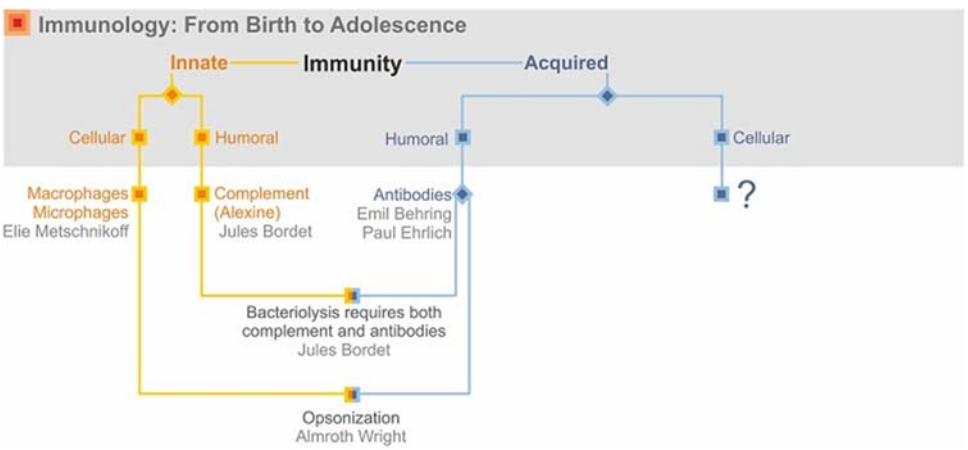

Fig. 1.1 Types of immunity (Kaufmann, 2019) different immune responses. *(From Kaufmann, S. H. E. (2019). Immunology's coming of age.* Frontiers in Immunology, 10. *https://doi.org/10.3389/fimmu.2019.00684.)*

structures, known as pathogen-associated molecular patterns (PAMPs). Examples of PAMPs involved in the identification of viral infections include double-stranded RNA, lipopolysaccharides, and peptidoglycans (Ekwemalor et al., 2023). Various PRRs, such as Toll-like receptors (TLRs), C-type lectin receptors (CLRs), nucleotide-binding oligomerization domain-like receptors (NLRs), retinoic acid-inducible gene-I-like receptors (RLRs), and AIM2-like receptors (ALRs), exhibit distinct and specific binding preferences for different microorganisms (Wicherska-Pawłowska et al., 2021).

Innate immunity also relies on cellular components such as macrophages, dendritic cells, natural killer cells, and neutrophils, which contribute to the rapid recognition of diverse threats, regardless of previous exposure (Fig. 1.2). The features of innate immunity can be categorized as barrier defense, the complement system, inflammation, and innate immune cells. Barrier defense includes anatomic barriers formed by cells lining the skin, airways, and gut, as well as physiological barriers, such as temperature, low pH, and chemical mediators (Pelz & Wechsler, 2019). The complement system, which is part of the internal defense, consists of a multitude of plasma proteins that interact with each other to enhance the phagocytosis of foreign cells (opsonization) and induce inflammatory responses to combat infections (Rôças & Siqueira Jr, 2022). Inflammatory responses manifest as erythema, edema, heat, and pain and are triggered after the activation of barrier and complement defenses. Innate immune cells and pattern recognition receptors are influenced by the release of cytokines, which act as regulatory signals

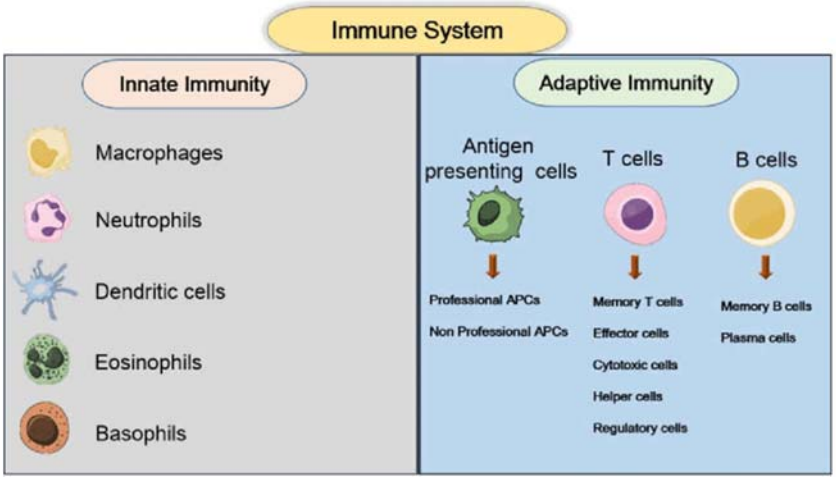

Fig. 1.2 Various cellular components of immune system (Surendran et al., 2018) cells of immune system. *(From Surendran, S. P., Moon, M. J., Park, R. & Jeong, Y. Y. (2018). Bioactive nanoparticles for cancer immunotherapy.* International Journal of Molecular Sciences, 19*(12).* https://doi.org/10.3390/ijms19123877*.)*

controlling the initiation of inflammatory responses to pathogens and injuries (Wu & Lu, 2019). Mononuclear phagocytes, such as macrophages and dendritic cells, primarily produce cytokines related to innate immunity. However, T lymphocytes, natural killer cells, endothelial cells, and mucosal epithelial cells can also generate cytokines in response to PAMPs, including inflammatory cytokines such as IL-1, IL-6, IL-8, and TNF cells (Mahapatro, 2021).

The adaptive immune response, also known as acquired immunity, differs from the innate immune response in terms of its timing and the involvement of specific immune cells, such as B cells, T cells, and antigen-presenting cells (APCs). Unlike the rapid response of innate immunity, the adaptive immune response takes time to identify, activate, and proliferate the necessary cells (Rastogi et al., 2022). It is initiated by antigens and is typically activated several days after exposure to infection.

2.2 Adaptive immune response

The adaptive immune response relies on antigen-specific lymphocytes and the development of immunological memory (Deets & Vance, 2021). When antigens are encountered, B cells and T cells are activated by APCs. Helper T cells, characterized by the CD4 protein, play a crucial role in activating immune cells to combat infected hosts by recognizing antigens presented by MHC class II molecules (Hua & Hou, 2020). In turn, infected host cells stimulate the maturation of B cells. Cytotoxic T cells recognize antigens presented by MHC class I and are capable of destroying virus-infected cells and releasing signals that activate macrophages and natural killer cells (Ghasemi et al., 2023).

B cells express unique antigen-binding receptors (Wiggins et al., 2021). When these receptors recognize specific antigens, the B cells produce antibodies that can bind to the antigens. These antibodies can be either expressed on the cell surface or released. Immune cells undergo phagocytosis and eliminate pathogens targeted by the antibodies. While some B and T cells die after the infection is cleared, others remain, providing long-term immunity to a particular infection or disease (Holborough-Kerkvliet et al., 2023). This immune system allows the body to mount a quicker and more effective response when it encounters a similar antigen in the future.

Different pathogens require specific response mechanisms to ensure the detection of their unique receptors. B cells primarily bind to bacteria and antigens present on the body's exterior, while T cells detect viruses and antigens present inside infected cells (Shepherd & McLaren, 2020). Despite their specificity, many of the effector mechanisms used to eliminate pathogens in the adaptive immune response are similar to those employed by the innate immune response.

The adaptive immune response can be categorized into two types: cell-mediated and humoral. Cell-mediated responses involve cytotoxic T cells, which have the ability to destroy cells that have been infected by pathogens. These T cells release signals that cause infected cells to undergo apoptosis, a form of cell death. The signals are often released via

perforin, which creates holes in the cell membrane, leading to an influx of water and ions that destroy the cells (Rühl & Broz, 2022). This process not only eliminates the infected cells but also reduces the chances of pathogen replication within them. The activation of cytotoxic T cells can be triggered by the presentation of antigens on infected cells, indicating the presence of a pathogen.

Macrophages also play a role in stimulating cytotoxic T cells. They engulf and process pathogens, presenting antigens from the pathogens on their cell surface. T helper cells, when activated by macrophages, release signals that stimulate cytotoxic T cells. These cytotoxic T cells continue to target pathogens present in infected cells, thereby amplifying the immune response (Chu et al., 2022). Helper T cells are also involved in the humoral response, where they assist B cells. When an antigen is presented on the membrane of a macrophage, it binds to a T helper cell, triggering the production of antibodies by B cells. Antibodies, Y-shaped proteins, have antigen-binding regions that allow them to bind to specific antigens (Bansia & Ramakumar, 2023). These antibodies can be found in saliva, mucous, blood serum, and other bodily fluids. Once an antibody binds to an antigen, it deactivates the pathogen, preventing its replication and growth. B cells can also be activated by free antigens they come into contact with. Both cell-mediated and humoral responses involve the presence of memory (Yue et al., 2021).

3. Antigen processing and presentation

Antigen processing and presentation are integral parts of adaptive immunity. They involve the degradation of antigens and their presentation on major histocompatibility complex (MHC) molecules. This process aids T cells in recognizing antigens present on the cell surface, which in turn contributes to the production of antibodies by B cells (Han et al., 2023). $CD4^+$ T cells rely on antigen-specific receptors and MHC molecules for their function, while $CD8^+$ T cells require MHC recognition to eliminate virus-infected cells. MHC molecules are divided into two classes: MHC class I and class II (Sun et al., 2022) Class I molecules present antigen peptides to $CD8^+$ T cells, while class II molecules present antigen peptides to $CD4^+$ T cells (Kotsias et al., 2019).

In MHC class I molecules, cytosolic proteins are transported to the proteasome, where they are degraded into smaller peptides of approximately 15 amino acids. These peptides are then transported to the endoplasmic reticulum by the transporter associated with antigen processing (TAP). In the endoplasmic reticulum, TAP collaborates with MHC class I molecules, which are associated with several helper proteins. Once the MHC class I molecules bind permanently to a peptide fragment, the TAP transporter and helper proteins dissociate (Praest et al., 2019). The antigen-loaded MHC class I molecule is then released through vesicle formation and travels to the cell surface via the Golgi apparatus. The vesicle membrane fuses with the plasma membrane, releasing the antigen-MHC class I complex. This complex can be recognized by the effector $CD8^+$ T cells.

In the case of the MHC class II complex, exogenous antigens are taken up by cells through endocytosis. These antigens interact with MHC class II molecules within endosomes. Initially, a single molecule occupies the binding site of MHC class II molecules, but helper cells facilitate the exchange of the small molecule with available antigens (Agerer et al., 2021). The vesicle containing the antigen-MHC class II complex then fuses with the plasma membrane at the cell surface. The antigen is subsequently recognized by $CD4^+$ T helper cells.

Antigens presented by MHC class I molecules are endogenous antigens derived from normal cells, including self-antigens or neoantigens. Some endogenous antigens may also contain viral components from infected cells. MHC class II molecules, on the other hand, present exogenous antigens derived from outside the cell, such as extracellular bacteria (Rock et al., 2016). The process of antigen presentation and processing by MHC class I and class II molecules is a key feature of adaptive immunity.

The function of immune cells is regulated through gene expression and immune genes. When a person is immunodeficient or immunocompromized, their immune system's defense mechanisms are impaired. Immunodeficiency prevents the individual from effectively fighting against infections and diseases, and as a result, they may develop autoimmune disorders such as multiple sclerosis, myasthenia gravis, pernicious anemia, reactive arthritis, rheumatoid arthritis, and Sjögren's syndrome, among others.

4. Immunodeficiency

Immunodeficiency refers to a condition in which the immune system's ability to defend the body against infections and diseases is compromised. The proper functioning of immune cells is regulated by gene expression and immune genes. When a person is immunodeficient, their immune system is weakened, leading to increased susceptibility to infections and a reduced ability to combat pathogens effectively (Sánchez-Ramón et al., 2019). It is important to note that immunodeficiency does not directly cause autoimmune disorders but can contribute to their development in some cases.

Autoimmune disorders occur when the immune system mistakenly attacks healthy cells and tissues in the body. Examples of autoimmune disorders include multiple sclerosis, myasthenia gravis, pernicious anemia, reactive arthritis, rheumatoid arthritis, and Sjögren's syndrome, among others. While immunodeficiency does not directly cause autoimmune disorders, the compromised immune system in immunodeficient individuals may contribute to the dysregulation of immune responses, leading to the development of autoimmune conditions (Mosanya & Isaacs, 2019).

Immunodeficiencies can be categorized into two types: primary (congenital) and secondary. Primary immunodeficiencies are typically genetic disorders that a person is born with. These conditions arise from inherited mutations in genes involved in immune function, leading to impaired immune responses (Amaya-Uribe et al., 2019). Secondary

immunodeficiencies, on the other hand, are acquired later in life and are more common than primary immunodeficiencies. Secondary immunodeficiencies can occur as a result of various factors, such as infections (e.g., HIV/AIDS), certain medications, malnutrition, or other underlying diseases. In secondary immunodeficiencies, a weakened immune system caused by an infection or disease can further worsen immune function and lead to the development of additional immune disorders (Vaillant & Qurie, 2022).

It is important for individuals with immunodeficiencies to work closely with healthcare professionals to manage their condition and reduce the risk of infection. Treatment options may include immunoglobulin replacement therapy, antiviral medications, vaccinations, and avoiding potential sources of infection (Katragkou et al., 2018). Additionally, ongoing research in immunology aims to understand the underlying mechanisms of immunodeficiencies and develop targeted therapies to improve immune function in affected individuals.

5. Autoimmune disorders

In an autoimmune disorder, the body's immune system is unable to distinguish between healthy tissue and potentially harmful antigens (Morton Cuthrell et al., 2022). As a result, the immune system mistakenly targets and attacks normal tissues alongside harmful antigens (Mezgebu et al.). While the exact causes of autoimmune disorders are not fully understood, many researchers propose that they may arise from factors such as microbial infections (bacteria and viruses) that disrupt the immune system's ability to recognize what is harmful to the body and what is not (Fugger et al., 2020).

Autoimmune disorders can lead to various adverse effects, including abnormal organ growth, changes in organ function, and tissue damage (Duan et al., 2019). It is possible for an individual to have one or more autoimmune diseases simultaneously. Moreover, it is not uncommon for individuals with one autoimmune disorder to develop another. These disorders can affect one or several organs (Morton Cuthrell et al., 2022). Common areas affected by autoimmune disorders include, but are not limited to, connective tissues, endocrine glands, blood vessels, joints, muscle cells, red blood cells, and the skin (Malavika et al., 2023).

While the specific symptoms experienced may vary depending on the particular autoimmune disorder, there are certain symptoms that are commonly reported across many diseases. These symptoms include fatigue, body aches, rashes, nausea, headaches, and dizziness.

According to recent studies on the prevalence of autoimmune disorders, disorders are more common in women than in men, with a ratio of 2 to 1 (Angum et al., 2020). Furthermore, many women develop autoimmune disorders during pregnancy or significant hormonal changes. The reasons for this gender disparity and the factors contributing to autoimmune disorders are still subjects of ongoing research (Kronzer et al., 2020).

While some autoimmune disorders have a genetic component, such as lupus and multiple sclerosis (MS), others are not hereditary (Borba et al., 2019). Additionally, even if a disorder runs in a person's family, it does not necessarily mean that they will develop the exact same disorder. Although the risk of developing the disorder is higher in these cases, it is not a guarantee. It is important to note that autoimmune disorders are not contagious, so being in contact with someone who has an autoimmune disorder does not mean that an individual will contract the disorder (Delogu et al., 2011).

At present, there is no known cure for autoimmune disorders. However, when diagnosed with an autoimmune disease, immunologists and physicians focus on treating the patient's symptoms rather than targeting the underlying cause of the disorder (Schiffenbauer & Miller, 2020). Therefore, treatment plans are unique to each individual, taking into account their reported symptoms, genetics, and a wide range of external and internal factors. The variability in how individuals experience autoimmune disorders underscores the importance of further research in immunology. A comprehensive understanding of immunology is crucial for advancing treatment and making new discoveries, especially in the field of autoimmune disorders.

6. Hypersensitive reactions

Hypersensitivity refers to undesirable or harmful reactions of the immune system. There are four types of hypersensitive reactions, each characterized by different mechanisms and immune components (Fig. 1.3) (Vaillant, Goyal, et al., 2023).

Type I hypersensitivity reactions are associated with allergens and can also result in anaphylactic responses. These reactions involve the production of immunoglobulin E

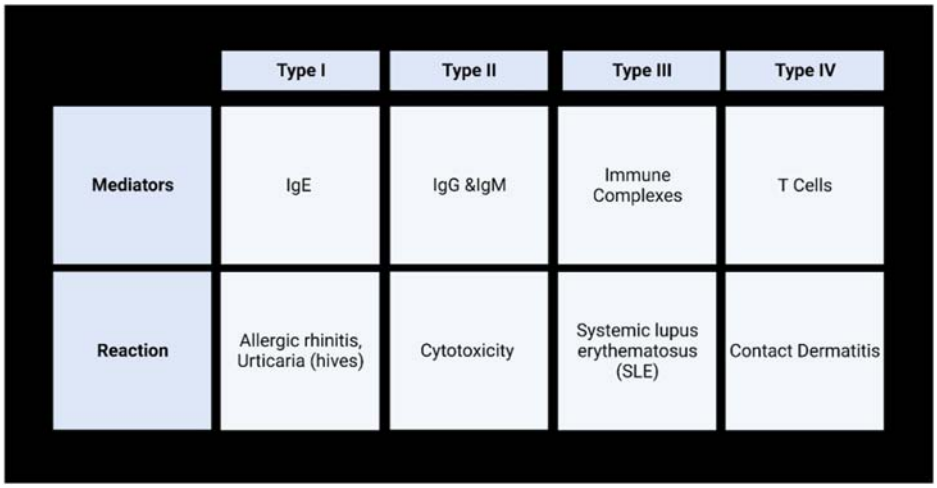

Fig. 1.3 Types of hypersensitivity reactions hypersensitive reactions.

(IgE) antibodies by the immune system when exposed to allergens such as pollen, animal dander, or substances causing contact dermatitis (Abbas et al., 2023). The IgE antibodies bind to mast cells and basophils, which release histamine upon activation. Histamine release leads to inflammation and can cause allergic rhinitis, urticaria (hives), asthma, and other allergic reactions (Patel & Mohiuddin, 2023). The most severe manifestation of a type I hypersensitivity reaction is anaphylaxis, which can be life-threatening and affect the respiratory and circulatory systems. Prompt treatment with epinephrine (adrenaline) is crucial to counteract the allergic response (McLendon & Sternard, 2023).

Type II hypersensitivity reactions also involve antibodies, specifically immunoglobulin G (IgG) and immunoglobulin M (IgM). In this type of reaction, IgG and IgM antibodies recognize and bind to antigens on the surface of host cells, leading to cell damage and degradation. This process is referred to as "cytotoxicity" (Marwa & Kondamudi, 2023). Type II hypersensitivity reactions can occur when the immune system mistakenly recognizes self-antigens, contributing to the development of autoimmune disorders (Bajwa & Mohammed, 2023).

Type III hypersensitivity reactions are characterized by the formation of immune complexes, which consist of multiple antibodies binding to several antigens. These immune complexes can deposit in blood vessel walls, triggering a cascade of events that lead to the formation of a membrane attack complex and subsequent cell death (Usman & Annamaraju, 2023). Additionally, immune complexes can induce neutrophil degranulation, releasing granules that cause severe cell damage. Type III hypersensitivity reactions are associated with widespread inflammation and damage. An example of a type III hypersensitivity reaction is systemic lupus erythematosus (SLE), where antibodies bind to self-DNA or self-proteins, contributing to the development of the autoimmune disorder (Vaillant, Vashisht, et al., 2023).

Type IV hypersensitivity reactions differ from the other three types as they are cell-mediated and regulated by T cells (Marwa & Kondamudi, 2023). Unlike types I, II, and III, which involve antibodies causing damage to host cells, type IV reactions are driven by T cells directly causing damage. Type IV hypersensitivity reactions are also known as "delayed hypersensitivity" because symptoms take time to appear after exposure (Vaillant, Vashisht, et al., 2023). Examples of type IV hypersensitivity include reactions to latex, poison ivy, and contact dermatitis (Marwa & Kondamudi, 2023).

Understanding the different types of hypersensitivity reactions is crucial for diagnosing and managing immune-related disorders and developing appropriate treatment strategies.

7. Vaccines and immunotherapy: Principles and applications

The field of vaccinology, which combines immunology and biotechnology, has been continuously advancing due to the prevalence of various infections and diseases (Oli et al., 2020). The study of vaccinations and the development of immunizations against

diseases were initiated by the English doctor Edward Jenner, who made significant contributions, particularly in relation to the smallpox virus (Czinn & Hoenig, 2023). Immunization can be achieved through active or passive immunity.

Active immunity is acquired naturally when an individual becomes infected and is directly exposed to an antigen (Grubbs & Kahwaji, 2023). In this process, the host cells generate protective immunity. Similar to the adaptive immune response, active immunity relies on immunologic memory, which involves B and T cells recognizing pathogens. Immunologic memory is essential for two reasons (Deets & Vance, 2021): firstly, it provides long-term immunity, allowing the immune system to respond swiftly to external antigens and antibodies attempting to enter the host cells. Secondly, memory cells are pathogen-specific, enabling an immediate immune response upon encountering a previously encountered pathogen (Zhang et al., 2021).

Vaccines play a crucial role in active immunity as they provide a controlled way to stimulate an immune response. When a person receives a vaccine, the immune system is triggered to mount a response without causing the actual illness. This allows the development of immunologic memory, providing the benefits of exposure without the associated risks of natural infection (Zimmermann & Curtis, 2019).

Passive immunity occurs when an individual receives second-hand immunity from another person who is already immune. Unlike active immunity, passive immunity is short-lived as there is no replenishment of antibodies. Maternal antibodies transferred across the placenta or through breast milk are examples of passive immunity (Langel et al., 2022). Another example is the use of immunoglobulin treatments, or intravenous immunoglobulin (IVIG), to treat immunodeficiencies, autoimmune disorders, and inflammatory conditions (Yaqinuddin et al., 2021). Antibodies for such treatments can be obtained from animals or synthesized in laboratories. IVIG is often used in patients with antibody deficiencies who require immune support. Antibodies are derived from the plasma membrane of healthy donors. For example, infants born to mothers with hepatitis B may receive both treatment and vaccination to prevent infection. Immunoglobulin treatments contribute to the management of immunodeficiencies and help normalize immune function in immunocompromized individuals (Arumugham & Rayi, 2022).

A wide range of vaccines have been developed, and others are currently under development or undergoing clinical trials. Each vaccine is distinct in its nature and efficacy in treating diseases and infections. Various types of vaccines include live attenuated vaccines, inactivated vaccines, etc. Vaccines may contain weakened versions of the original pathogenic agents. Examples include vaccines for measles, mumps, and rubella (Kumar, 2019). These live vaccines elicit strong antibody responses and provide long-term immunity, often requiring only one or two doses. Inactivated vaccines, on the other hand, are

created by killing pathogens through heat, radiation, or chemicals. Well-known examples are influenza vaccines. Inactivated vaccines result in weaker immune responses compared to live vaccines such as those for measles or mumps and often require additional booster shots to maintain immunity (Burghate & Mundada, 2023). Other types of vaccines include toxoid vaccines, which stimulate the immune response against bacterial toxins, as seen in diphtheria and tetanus vaccines, and conjugate vaccines, where antigens or toxins from microbes are linked to polysaccharides on the outer coating of the microbes (Ricci et al., 2023). The influenza type B (Hib) vaccines are examples of conjugate vaccines. Recent discoveries and ongoing research demonstrate the close connection between the study of immunology and the progress in vaccines. Vaccines initiate an immune response in the body, allowing it to fight off pathogens and retain information about specific antigens (Umar et al., 2021). If the antigen is encountered again, the immune system has already established a defense mechanism. Vaccines provide long-lasting immunity and play a crucial role in disease prevention (Fig. 1.4).

As emergent discoveries are constantly being made, it is evident that immunology is an emerging field of medicine and one whose progression furthers understanding of the immune system and various disorders, diseases, and infections. Whether it be to build herd immunity through developments in immunization, to progress immunotherapy treatments, or to study cures for autoimmune disorders, immunology is essential in a wide array of aspects of life. A progression in immunology is a progression in societal understanding of medicine.

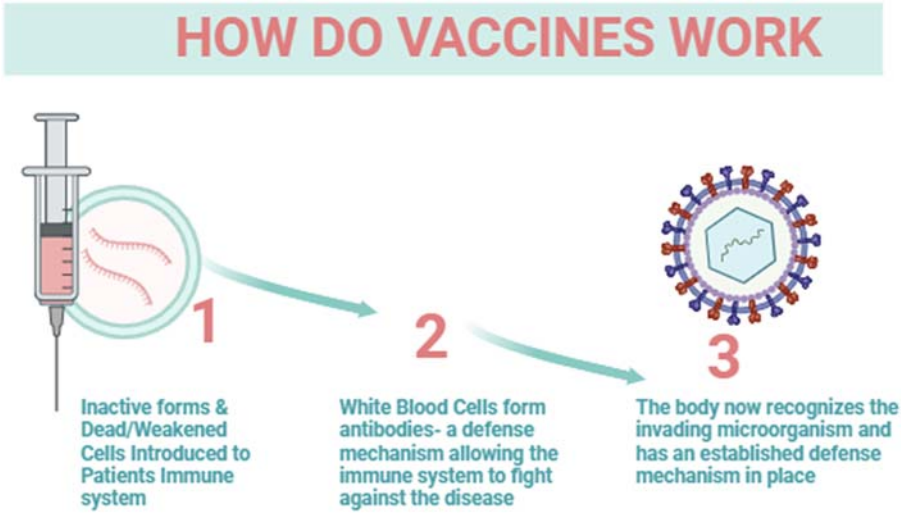

Fig. 1.4 Mechanism of action of vaccine mechanism of vaccine.

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CHAPTER 2

Cells of the immune system and their multifunctional roles

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1. Introduction

The immune system is a network of cells, substances, and mechanisms that protect the skin, nasal passages, intestinal tracts, and other organs against foreign antigens. This includes viruses, cancerous cells, poisons, and microbes (organisms such as bacteria, fungi, and parasites) (Parham, 2014). Furthermore, it is capable of distinguishing between foreign molecules and the cells and proteins of the body. To protect the body from outside invaders, the immune system is made up of various components. Two basic components of the immune system are the thymus gland and bone marrow. It is the bone marrow that produces all blood cells in the body, including T and B lymphocytes, making it an important part of the immune system (Tokoyoda et al., 2004). Innate immunity and adaptive immunity can be thought of as the immune system's two main "lines of defense" (Ajana, 2021). These extra "defences" go beyond the chemical and structural barriers that keep infection at bay. The initial line of defense against an invading infection is innate immunity. This nonspecific (antigen-independent) defense response is initiated by the host shortly after or within hours of coming into contact with an antigen. The lack of immunologic memory in the innate immune system prevents it from recognizing or "memorizing" the same infection if the body comes into contact with it again in the future (Pinto et al., 2022). Adaptive immunity is differentiated by the ability to remember, which allows the host to generate a faster and more effective immune response following future antigen exposure (Shinde et al., 2022). Innate and adaptive immunity are complementary rather than antagonistic host defense systems, and deficiencies in either system make the host more susceptible or produce incorrect responses (Meijer, 2016). The differences between innate and adaptive immunity are depicted in Table 2.1. This review provides a detailed view of innate and adaptive immunity.

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Table 2.1 Characteristics and function of some important cells involved in immunity.

Cell(s)	Percentage (%)	Lifetime	Target	Functions
Neutrophils	40–75	Few (06) hours to a few days	Bacteria, fungi	Degranulation and phagocytosis
Eosinophils	1–6	8–12 days	Various allergic tissues, parasites	Release of growth factors, cytokines and enzymes and degranulation
Basophils	<1	Few hours to a few days	Various allergic tissues	Release of histamines, cytokines, and enzymes and degranulation
Mast cells	Similar in tissues	Varies from months to years	Various allergic tissues, parasites	Release of histamines, cytokines, and enzymes and degranulation
Macrophages	Varies	Varies from months to years	Different targets	Antigen presentation to T cells and phagocytosis
Lymphocytes (T cells)	20–40	Varies from weeks to years	The virus infected tumor cells, intracellular bacteria	Immune response mediators and cell destruction
Monocytes	2–6	Varies from a few hours ta o few days	Different targets	Differentiate into macrophages and dendritic cells to elicit an immune response
Natural killer cells	15	Varies from 7 to 10 days	Tumor cells, viruses	Induction of apoptosis through the release of perforin and granzymes, destruction of infected cells and tumor rejection

2. Innate immunity

Innate immunity, which is older in evolutionary time than acquired immunity, dominates in plants, fungi, insects, and early multicellular animals. The first line of defense against invading infections is the innate immune system (Tomar & De, 2014). As a result of the development of the innate immune system, the host is protected from toxins, bacteria, fungi, viruses, and parasites. In fact, it dates back to before the acquired or adaptive immune responses (Goldsby et al., 2000). Anatomical constraints, phagocytes (such as neutrophils, monocytes, and macrophages), inflammatory-related serum proteins (such as complement, C-reactive protein, lectins like mannose-binding lectin, and ficolin's), as well as antimicrobials observed on the surfaces and granules of phagocytes, are all factors that prevent the spread of bacteria (Aristizábal & González, 2013). A signaling cascade is initiated when the invading pathogen interacts with the host, enhancing the immune response and activating particular mechanisms. Generally, the natural immune response has three purposes: (1) to prevent infection; (2) to remove invasive pathogens; and (3) to activate the acquired immune response, according to Aristizábal and González (2013). Cytokines and chemokines facilitate the rapid recruitment of immune cells into areas of infection and inflammation. Several defense systems, as well as local cellular responses to infection or injury, are activated by cytokine production during innate immunity (Parker & Prince, 2011). In the early stages of bacterial infection (IL-6), tumor necrosis factor (TNF), interleukin 1 (IL-1) and interleukin 6 (IL-6) are key inflammatory cytokines. Several infections can be eliminated by activating these cytokines, which initiate local inflammation and promote cell recruitment. The onset of fever can be influenced by them. Due to their connections to inflammatory and autoimmune diseases, these inflammatory cytokines are important therapeutic targets (Gunther et al., 2011). As part of the complement system, bacteria and other pathogens are recognized and opsonized (coated). Additionally, it can recruit and activate antigen-presenting cells to trigger the adaptive immune response. Innate immunity is composed of cells and proteins in the body that are always prepared to attack bacteria when infected (Marshall et al., 2018). Our innate immune system is composed of Phagocytes (macrophages and neutrophils), dendritic cells, mast cells, basophils, eosinophils, natural killer (NK) cells, and innate lymphoid cells (Fig. 2.1) (Molina et al., 2010). Neutrophils and macrophages are the two main cell types that makeup phagocytes. They both aim to engulf (phagocytose) germs and eliminate them via various bactericidal techniques. Neutrophils possess granules and enzyme pathways in addition to their capacity for phagocytosis, which helps them get rid of harmful germs. Macrophages have a longer lifetime than neutrophils and are involved in phagocytosis as well as antigen presentation to T cells (Warrington et al., 2011).

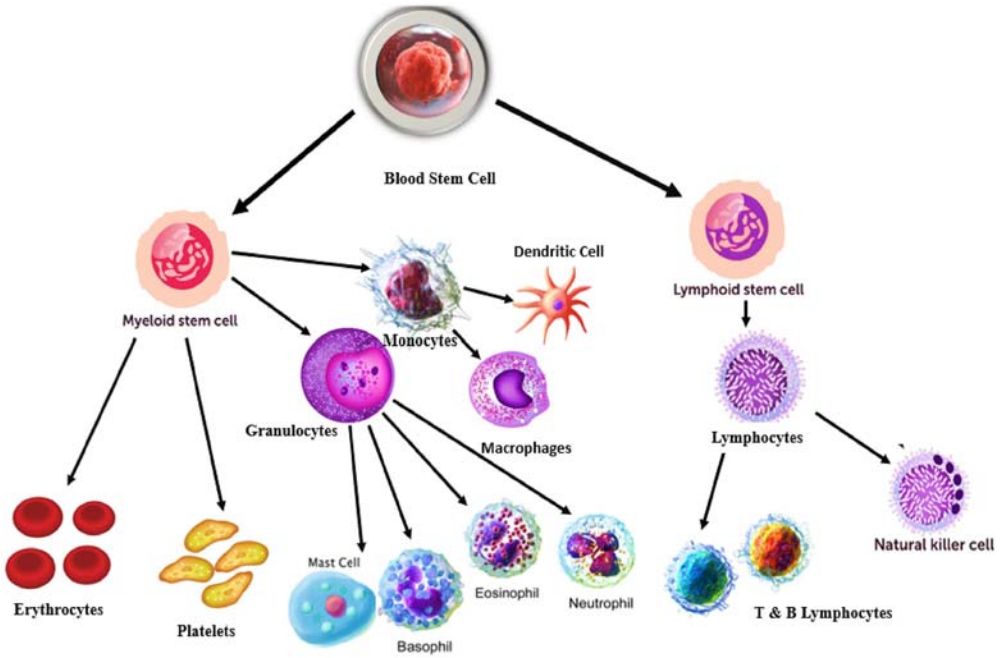

Fig. 2.1 Different cells of the immune system cells of immune system.

2.1 Cells involved in innate immunity and their role

Macrophages, neutrophils, natural killer cells, dendritic cells, basophils, and eosinophils are among the cells that contribute to innate immunity. A cell's function in innate immunity is to respond quickly and broadly to pathogens that are invading the body (Tosi, 2005). Instead of individual antigens, they are able to identify and react to broad patterns of infections. They are capable of rapidly mobilizing and enlisting more immune cells to the infection site, phagocytosing and eliminating pathogens, and triggering the adaptive immune response by presenting antigens to T cells (Chaplin, 2010). Leukocytes known as granulocytes have enzyme-containing granules in their cytoplasm. Examples of granulocytes include neutrophils, basophils, and eosinophils (Chaplin, 2006).

2.1.1 Neutrophils

The initial responders of the innate immune system are thought to be neutrophils. They have granules in them that have a poisonous nature and will obliterate any pathogen that comes into contact with them. Given that their cytoplasm is filled with granules, neutrophils, which are phagocytic cells, are also referred to as granulocytes (Hampton et al., 1998). When bacteria and fungus come into touch with these granules, their growth stops or they die. Around 100 billion new neutrophils are produced daily by the bone marrow of a typical healthy adult. Since there are so many of them in circulation at

any given moment, neutrophils are often the first cells to reach the site of infection (Dale & Welte, 2001). Neutrophils and macrophages are cells that live in tissues and circulate through the blood, keeping an eye out for any concerns. Both cells have the ability to "eat" germs and, if necessary, interact with other immune cells (Sompayrac, 2022).

2.1.2 Macrophages

Innate immunity, the body's initial line of defense against invasive infections, is greatly aided by macrophages. These immune cells are produced from bone marrow-derived monocytes and are a subset of the mononuclear phagocyte system (Xiu & Jeschke, 2013). Once triggered by the presence of infections, macrophages carry out a number of tasks to get rid of the invaders. They offer antigens to trigger the adaptive immune response, phagocytose (engulf and break down) microorganisms and cellular debris, and produce cytokines to draw other immune cells to the infection site. Considering that they create growth factors and extracellular matrix proteins, macrophages also contribute to tissue repair and remodeling (Murray & Wynn, 2011). They also take part in the elimination of apoptotic cells, which is necessary for preserving tissue homeostasis. Generally speaking, macrophages are crucial elements of the innate immune system, offering a vital line of defense against invasive infections and supporting tissue repair and upkeep (Esteban et al., 2015).

2.1.3 Mast cells

Mast cells are an immune cell type that is essential to the immunological response, especially in allergy responses and parasite defense. Mast cells produce granules containing histamine, heparin, and different cytokines and chemokines when they come into contact with an allergen or pathogen (Rao & Brown, 2008). These mediators can widen blood arteries and make them leaky, which can induce inflammation and draw additional immune cells to the infection site. Mast cells are triggered during allergic responses when IgE antibodies connect to their surface receptors, releasing histamine and other mediators that induce symptoms including itchiness, swelling, and breathing difficulties (Anvari, 2019). Mast cells can identify and react to certain antigens on the surfaces of parasites, which allows them to play a part in parasite defense. Mast cells secrete granules carrying enzymes that can directly kill parasites when activated by parasites, as well as cytokines that draw in other immune cells to aid in the infection's eradication. Mast cells play a significant role in the immune response overall, helping to fight off infections and set off allergic responses (Mukai et al., 2016).

2.1.4 Eosinophils

White blood cells known as eosinophils are involved in the innate immune response, especially in the defense against parasites and in allergic responses. Eosinophils produce a wide range of mediators when stimulated, including cytokines, chemokines, and

cytotoxic granules that contain enzymes that can eradicate parasites (Cruvinel et al., 2010). Eosinophils are strictly controlled to prevent collateral damage since these granules also contain proteins that might harm the host tissues. Eosinophils are especially efficient against helminth parasites because they are too big for other immune cells to phagocytose (Shamri et al., 2011). Eosinophils can attach to the surface of helminths and produce cytotoxic granules that can either kill the parasites directly or immobilize them so that other immune cells can more easily attack them. They have highly poisonous proteins that are lethal to any bacterium or parasite they come into touch with (Male et al., 2020). Granulocytes are called eosinophils to attack multicellular parasites. Toxic proteins and free radicals are used during allergic responses, which results in tissue damage (Kiboneka, 2021). Eosinophils are drawn to the inflammatory site in allergic responses by the production of cytokines, notably interleukin-5 (IL-5). Eosinophils are specialized cells that are part of the innate immune system that help the body fight parasite infections and are also involved in allergy responses (Waddell, 2012).

2.1.5 Basophils

A kind of white blood cell known as a basophil is involved in innate immunity's numerous immunological responses, including allergy reactions and parasite protection (Cruvinel et al., 2010). Basophils get triggered during allergic responses when IgE antibodies connect to their surface receptors. Their activation results in the production of a number of mediators, including histamine, prostaglandins, and leukotrienes, which enhance vascular permeability, produce vasodilation and trigger smooth muscle contraction (Altman & Chang, 2013). These reactions may result in allergy symptoms such as swelling, redness, and itching. cytokines, notably interleukin-3 (IL-3), interleukin-5 (IL-5), and granulocyte-macrophage colony-stimulating factor, stimulate basophils to defend against parasites (GM-CSF). Once engaged, they emit mediators that are similar to those seen in allergic responses and can aid in the death or immobilization of parasites. Moreover, basophils aid in attracting additional immune cells to the area of inflammation (Boyce, 1997). They may produce chemokines that draw eosinophils and other immune cells to the location of the inflammation. They target parasites that are multicellular. They also produce histamine, much like mast cells do. Granulocytes called basophils also go after multicellular parasites. Histamine is released by basophils similarly to mast cells (Boyce, 1997). Overall, basophils have a role in allergy responses, parasite defense, and the attraction of more immune cells to the site of inflammation, which all contribute to the innate immune response (Liaskou et al., 2012).

2.1.5.1 Natural killer cells

A kind of lymphocyte known as natural killer (NK) cells is crucial to the innate immune response, especially in the fight against viruses and cancerous cells. NK cells, or natural killer cells, do not actively combat infections (Trinchieri, 1989). NK cells are able to

identify and eliminate malignant or virus-infected cells. They achieve this by identifying aberrant cells and attaching to them. These abnormal cells may have reduced expression of major histocompatibility complex (MHC) molecules, stress-induced chemicals, or certain receptors that are recognized by NK cells (Rabinovich et al., 2003). When NK cells bind to a target cell, they release cytotoxic granules that trigger apoptosis in the target cell (programmed cell death). Moreover, cytokines that are released by NK cells might aid to mobilize and draw in additional immune cells to the infection site. Moreover, NK cells are involved in the control of the adaptive immune response (Castriconi et al., 2009). For instance, they can interact with macrophages and dendritic cells to modify their activity and encourage T-cell activation. NK cells are crucial innate immune response effectors that provide quick and comprehensive protection against viruses and tumor cells as well as aid in activating and coordinating the adaptive immune response (Lanier, 2005).

2.1.5.2 Dendritic cells

Dendritic cells are situated in tissues that are typically the location of initial infection, recognize dangers and communicate with the rest of the immune system by presenting antigens (Iwasaki, 2007). They are essential for the processing and presentation of pathogen antigens to other immune cells, which can then result in an adaptive immune response (Lambrecht et al., 2001). Throughout the body's tissues, DCs are particularly prevalent in regions that come into touch with the outside world, such as the skin, respiratory, and gastrointestinal tracts. They have a unique shape that enables them to seize antigens and go to lymph nodes where they can expose these antigens to T cells and B cells (Hu & Pasare, 2013). A DC goes through a process known as maturation after it has captured an antigen, which involves the upregulation of costimulatory molecules and the production of cytokines that encourage T-cell activation. Once in the lymph nodes, the mature DC exposes the antigen to T cells (Toebak et al., 2009). In the early phases of infection, when they can quickly acquire and deliver antigens to trigger the immune response, DCs are particularly crucial. By deciding which antigens are given and encouraging the activation of particular T cell subsets, they are also crucial for starting and directing the adaptive immune response. When it comes to the acquisition, processing, and presentation of antigens as well as the beginning and regulation of the adaptive immune response, DCs are important innate immune effectors (Banchereau et al., 1998).

3. Adaptive immunity

The immune system that forms after being exposed to an antigen, whether through a disease or a vaccine, is known as adaptive immunity. Adaptive immunity occurs when an organism's immune system remembers a specific pathogen, allowing it to respond more effectively to that pathogen in the future. Adaptive immune systems rely heavily

on antibodies. When the innate immune system is unable to effectively combat an infection, this immune system element is sparked (Warrington et al., 2011). After an initial reaction to a particular illness, adaptive immunity accumulates immunological memory, resulting in a greater response to subsequent encounters with that pathogen (Bonilla & Oettgen, 2010). Long-lasting protection, possibly for the remainder of a person's life, can be obtained by adaptive immunity. White blood cells called lymphocytes are in charge of the adaptive immune response. An increased number of activated T and B lymphocytes target the invasive pathogen because their surface binding sites are tailored to the molecules on the pathogen. They can fight infections directly or produce antibodies that encourage pathogen phagocytosis and therefore cause the disease to cease (Delves & Roitt, 2000). In order to provide the host with long-term defense against reinfection with the same pathogen, adaptive immunity contains a memory; upon reexposure, this host memory will trigger a quick and effective response (Gasper et al., 2014). The major differences between the innate and adaptive immune responses are enlisted below (Table 2.2).

3.1 Cells involved in adaptive immunity

The adaptive immune system, in contrast to the innate immune system, relies on just 2 cell types: B cells and T cells (Fig. 2.1). B cells and T cells are lymphocytes that develop in the bone marrow from a particular class of stem cells known as multipotent hematopoietic stem cells. They must grow and become active after being created in the bone marrow. Each sort of cell takes multiple routes to develop into its ultimate, mature form (Uccelli et al., 2006).

3.1.1 B lymphocytes

B lymphocytes, sometimes called B cells, are white blood cells that play a crucial role in adaptive immunity. In the body, antibodies aid in the removal of antigens (foreign substances) by attaching to them (LeBien & Tedder, 2008). Among birds, B cells develop in the bursa of Fabricius, which is why "B" is abbreviated in B cells. More than 10 numbers of B cells with different antigenic specificities are produced by a random gene rearrangement in the bone marrow during B cell maturation. The remaining B cells are then eliminated using a membrane-bound antibody that detects self-components (Hartley et al., 1993). The B cell is activated when the antigen binds to its receptor, which is unique to each cell. In the fight against extracellular pathogens, such as bacteria and viruses moving through the blood or lymph, B cells are particularly crucial. These pathogens can be neutralized by antibodies when they attach to them, marked for destruction by other immune system cells, or activated by complement proteins, which can lyse the pathogen immediately (Galli & Calder, 2009). B cells collaborate with other immune system cells to coordinate and control the immune response in addition to their function in generating antibodies. For instance, they can interact with T cells to encourage their activation

Table 2.2 Innate immunity versus adaptive immunity: A summary.

Attribute	Innate immunity	Adaptive immunity
Response time	Fast: minutes or hours	Slow: days
Specificity	Confined to certain chemicals and molecular patterns linked to common diseases or foreign particles	Very accurate can discriminate between pathogen and nonpathogen structures and can detect small changes in molecular structures.
Major cell types	Macrophages, neutrophils, natural killer cells, dendritic cells, basophils, eosinophils	T lymphocytes, B lymphocytes, and other antigen-presenting cells
Key components	Antimicrobial peptides and proteins, such as toxic granules	Antibodies
Self versus nonself discrimination	As self vs. nonself, discrimination is the foundation of innate immunity, it must be flawless.	While less efficient than the innate immune system, categorization may still be accomplished rather successfully. A lack of self and other discrimination is the root cause of autoimmune diseases.
Immunological memory	None	Using memory could enable a speedier response to subsequent or reoccurring diseases.
Diversity and customization	Receptors employed are limited; they only identify antigen patterns and are common receptors. There are no additional receptors created to accommodate the immunological response.	Recombination of genes may be utilized to customize the recognition of epitopes and antigenic determinants, which is incredibly varied.

and differentiation as well as with dendritic cells and macrophages to encourage antigen presentation. The generation of antibodies and the coordination of immune responses against a variety of diseases make B cells essential effectors of the adaptive immune response (Kallies & Good-Jacobson, 2017).

3.1.1.1 B cell differentiation and activation

B lymphocytes are formed in the bone marrow. During the maturation phase, up to 100 trillion unique B cell clones can form, which is equivalent to the number of antigen receptors on T cells (Hofmeyr, 2001). T cell growth and tolerance are more known than the growth of B cells. Immature B lymphocytes are signaled to encourage their own death by apoptosis, which successfully wipes them out of the population when they

firmly bind to self-antigens generated on tissues. Clonal deletion is the name for this (Hofmeyr, 2001). Nevertheless, rather than being physically destroyed, B cells exposed to soluble antigens in the bone marrow undergo clonal anergy, rendering them incapable of functioning (Goodnow, 1992). Peripheral tolerance, a different mechanism, directly leads to T-cell tolerance. When mature B cells exit the bone marrow without coming into contact with self-antigen, peripheral tolerance develops (Goodnow et al., 1989). Th2 helper T cells are required to signal the majority of protein antigens in order for antibodies to be generated. B cells bind to self-antigens and die without being triggered by apoptosis signals from neighboring Th2 cells. In this way, T cells can have an impact on an adaptive immune response. The B cells become activated as soon as they bind with antigens and start the process of differentiating into plasma cells (Vinuesa et al., 2005). The differentiation process of plasma cells is therefore considered to be terminal. B cells are divided into three major types: memory, activated, and proliferating. There is no difference in behavior between memory T cells and memory B cells (MacLennan et al., 2003).

3.1.2 T lymphocytes

T lymphocytes, or T cells, are an essential component of the adaptive immune response. They are a particular variety of white blood cells that developed in the thymus gland after being created in the bone marrow (Gruver et al., 2007). Specific antigens, which are foreign substances that might elicit an immune response, are recognized by and dealt with by T cells. Helper T cells and cytotoxic T cells are the two primary subtypes of T cells. Helper T cells, often referred to as $CD4^+$ T cells, are essential for controlling the immune response because they instruct and activate other immune cells including macrophages and B cells. Antigen-presenting cells (APCs), such as dendritic cells and macrophages, deliver antigens to them that they detect, and they subsequently release cytokines that stimulate other immune cells (Miller, 2020). Cells that are infected with viruses or other intracellular pathogens are attacked and killed by cytotoxic T cells, sometimes referred to as $CD8^+$ T cells. They release cytotoxic chemicals like perforin and granzyme after recognizing antigens that are shown on the surface of infected cells, which causes the infected cells to undergo apoptosis (cell death) (Tomar & De, 2014).

3.1.2.1 T cell-mediated immune responses

The lymphocytes, which include T and B cells, are the main cells that regulate the adaptive immune response. T cells are particularly significant since they frequently also directly affect B cell immune responses in addition to a wide range of immunological responses. A two-chain protein receptor is used by T lymphocytes to recognize antigens. The most abundant and important of these are the alpha-beta T cell receptors (Fig. 2.2).

The T cell receptor is made up of two chains, each of which has two domains. As the amino acid sequence of this domain changes among receptors, it is called the variable

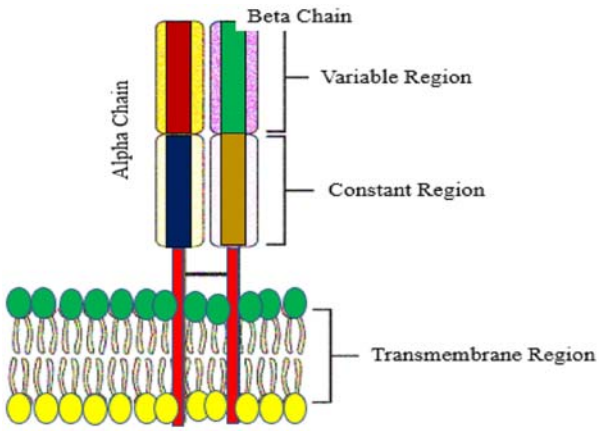

Fig. 2.2 Alpha-beta T cell receptor alpha-beta T cell receptor.

region domain and is located the farthest from the T cell membrane (Clevers et al., 1988). The constant area domain, however, exhibits less change. The molecular foundation for the variety of antigens the receptor may identify changes in the amino acid sequences of the variable domains. The terminal ends of both receptor chains make up the antigen-binding site of the receptor, and the amino acid sequences of those two regions work together to establish the receptor's antigenic specificity. Each T cell only generates one unique type of antigen, making them each specialized for just one thing (Schroeder et al., 2010).

4. Antigens

Being vast and complicated and made up of several antigenic determinants, pathogen antigens are often huge and complex. A receptor's ability to bind to an antigenic determinant (also known as an epitope) is restricted by the size of the receptor. Epitopes are tiny areas inside an antigen (Hajighahramani et al., 2017). Compared to protein antigens, antigenic determinants on carbohydrates are often less varied. Red blood cells (the ABO blood type antigens) and the walls of bacteria both contain carbohydrate antigens (Khatun et al., 2017). Antigens of proteins can take on a variety of three-dimensional shapes, making them difficult to detect by antibodies against viruses and worm parasites. The association between the antigen's structure and the complementary shape of the amino acids at the antigen-binding site explains the chemical basis of specificity (Parham, 2014) (see Fig. 2.3).

4.1 Antigen processing and presentation

Antigen processing is a complicated biological process that turns foreign substances such as bacteria or viruses into minute peptide fragments that immune cells in the body can detect

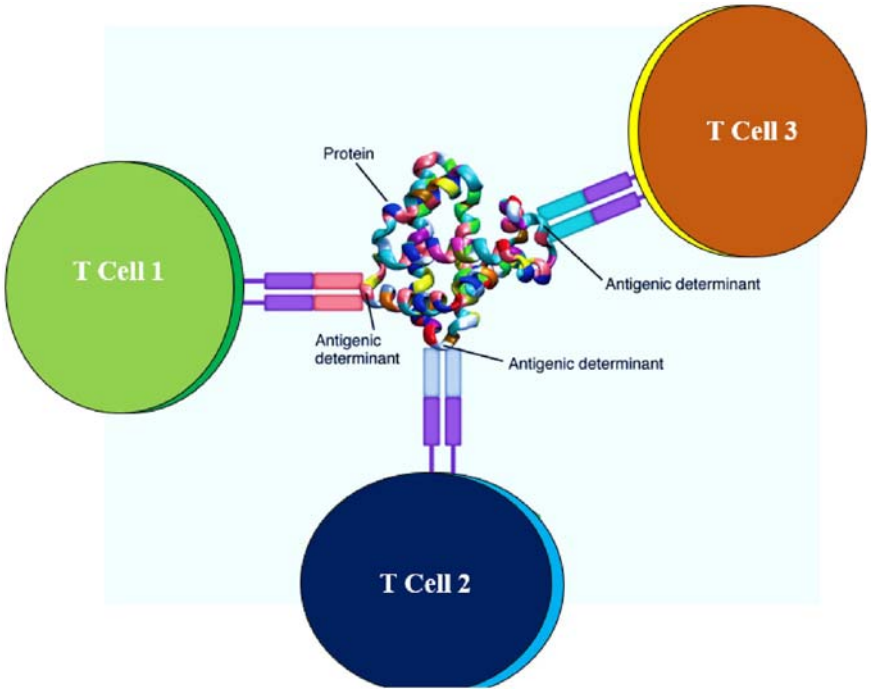

Fig. 2.3 Antigenic determinants antigenic determinants.

(Pishesha et al., 2022). This mechanism is required for the immune system to respond effectively to invading infections. The antigen peptide fragments are displayed on a major histocompatibility complex (MHC) molecule on the surface of the APC during antigen presentation (Jensen, 2007). The MHC molecule subsequently connects to a T-cell receptor (TCR) on the surface of the T cell, initiating a series of processes that result in the T cell becoming activated. Despite the fact that Fig. 2.3 shows direct interactions between T cell receptors and antigenic determinants, the method by which T cells recognize antigens is significantly more complex (Bridgeman et al., 2012). T cells do not recognize antigens that are cell-bound or free-floating on the surface of the pathogen (Leibach, 2005). Only antigens found on the surface of specialized cells known as antigen-presenting cells may be detected by them. The MHC gene family encodes these antigen-presenting molecules. When antigen fragments attach to an MHC molecule on a cell's surface, the antigen is recognized by antigen presentation by a T cell. Within the cell, MHC and antigen bond collectively, and their complex is what is sent to the surface (Porcelli & Modlin, 1999). MHC molecules can show a range of antigens in their peptide-binding clefts depending on the amino acid sequence. Along with the MHC protein, the T cell receptor physically recognizes the first peptide or carbohydrate fragment (Germain, 1994). MHC class I and MHC class II are two distinct MHC molecule

classes that are involved in antigen presentation. Although being made up of different gene combinations, they both have similar activities. Via a transport vesicle, they bring the prepared antigen to the cell's surface where they offer it to the T cell and its receptor (Alberts et al., 2002a,b). Yet, in order to display themselves on the cell surface, antigens from distinct disease types use several MHC classes and travel via various cell areas (Mantegazza, 2013). Nonetheless, the underlying process is the same. In order for T cells to recognize antigens, they must first be digested, transported into the cell's endomembrane system, and then expressed on the antigen-presenting cell's surface (Hansen & Bouvier, 2009). Intracellular antigens are typically produced by bacteria, viruses, and other intracellular parasites and pathogens. Before being carried to the cell surface by a transport vesicle, they engage with class I MHC molecules there (Schmid & Münz, 2007).

4.2 Professional antigen-presenting cells

Class I molecules are expressed by a variety of cell types to deliver intracellular antigens. The pathogen inside the cell as well as the cell itself may be eliminated as a result of these MHC molecules inducing a cytotoxic T-cell immune response. This is crucial when it comes to the virus, the most prevalent type of intracellular infection (Broere & Van, 2019). Every tissue in the body can be infected by viruses, hence all of these tissues must be able to express class I MHC in order for T-cell responses to occur. Class II MHC molecules, on the other hand, are only expressed in immune system cells, more especially in cells that influence other immune response arms. The term "professional" antigen-presenting cells are used to describe these cells in order to set them apart from those that carry class I MHC (Guermonprez et al., 2002). The three different categories of expert antigen presenters are B cells, dendritic cells, and macrophages. T cells are induced by macrophages to produce cytokines that improve phagocytosis (Franchimont, 2004). While dendritic cells also phagocytose infections, their primary job is to transport antigens to locally draining lymph nodes. The lymph nodes host the majority of T cell responses against pathogens of the interstitial tissues. Macrophages are cells that line mucosal surfaces like the lining of the skin and the nasopharynx, stomach, lungs, and intestines (Kastenmuller et al., 2012).

5. Humoral immune response

The humoral immune system's name comes from the fact that it involves chemicals that are present in body fluids or humor. Extracellular macromolecules such as secreted antibodies complement proteins, and specific antimicrobial peptides act as mediators for this type of immunity. The term humoral immunity refers to antibody production and its corresponding processes, including Th2 activation and production of cytokines, germinal center formation and isotype switching, affinity maturation and memory cell generation (Actor, 2011).

5.1 Complement system

In both acquired immunity and innate immune responses, the complement system is implicated. It is termed in such a way because its "complements" or aids in the removal of pathogens from an organism by antibodies and phagocytic cells. The general immune system components with role and functions of each component are enlisted in Table 2.3. The innate immune system's biochemical cascade aids in the removal of infections from an organism (Palanisamy et al., 2018). Cytolysis, chemotaxis, opsonization, immunological clearance, and inflammation are brought on by the activation of this system (Palanisamy et al., 2018). The mannose-binding lectin pathway, the alternative complement pathway, and the classical complement pathway are the three biochemical processes that initiate the complement system (Fig. 2.4) (Defendi et al., 2021). A homologous variant of the protease C3-convertase is generated by each of the three activation pathways. For activation of the classical complement pathway, antigen-antibody complexes are typically needed, while the alternative pathway is triggered by nonspecific immune responses, foreign material, pathogens, or damaged cells (Lachmann et al., 1984). An antigen or C3 hydrolysis can activate the mannose-binding lectin pathway that does not require antibodies (nonspecific immune response). It is a cascade of further cleavages and activations that occurs when the component C3 is cleaved and activated by C3-convertase through all three pathways. By binding to the surface of pathogens, C3b enables phagocytic cells to internalize them more effectively (Dunkelberger & Song, 2010). The three pathways of complement activation are shown below in Fig. 2.4.

6. Antibodies

Antibodies are components of humoral immunity. Antibodies can be found in blood, stomach and mucus discharges, as well as breast milk (Brandtzaeg, 2010). These bodily fluids include antibodies that attach to viruses and mark them for phagocyte destruction before they infect cells. When the antigen is present, these antibodies bind to it and circulate throughout the circulatory and lymphatic systems. To battle infection, the binding employs many techniques (Alberts et al., 2002a,b). Viruses and bacteria cannot be infected or attached to other cells by antibodies because antibodies attach to them and block their chemical processes. By clustering antigenic sites together, the antibodies can impair the functionality of particles with antigenic sites (Kapingidza et al., 2020). Activating the complement system, the antigen-antibody combination kills the antigen-carrying cell. Antigen-antibody complexes promote phagocytosis by attracting phagocytic cells, as reported earlier (Griffin et al., 1976). The presence of antibodies in mucus and on the skin causes inflammation and prevents pathogen assaults. Among the ways antibodies engage extracellular pathogens (such as receptors that "dock" them on host cells), they inhibit critical pathogen sites that increase their infectivity

Table 2.3 Immune system components glossary.

Component	General description
Antigen	Anything that could trigger the body's immune system to react. Bacteria, substances, poisons, viruses, and pollen are a few examples. Cancer cells and normal body cells both include antigens that might elicit an immunological response. Tumor cells develop from normal cells, but they produce "neoantigens" made of mutant self-protein and nonself-antigens. Adaptive immunity may be triggered by tumor antigens.
Antigen-presenting cell (APC)	Protein antigens can be converted into peptides by cells such as macrophages, dendritic cells, and B cells. These peptides can subsequently be delivered to T-cell receptors on the cell's surface together with major histocompatibility complexes.
Antibody (Ab)	Commonly known as an immunoglobulin (Ig). In reaction to fresh infections or vaccinations, the body might produce new antibodies.
Basophil	Basophils are granular phagocytic immune cells. Inflammation triggers the release of histamine by basophils during allergic responses.
B Lymphocyte	White blood cells called B lymphocytes are a specific kind that forms in the bone marrow and produces antibodies.
Cytokine	A particular kind of protein affects the immune system by either enhancing it or suppressing it. Cytokines can be created artificially in a lab or naturally in the body.
Dendritic cell	Antigen-presenting cells include dendritic cells (APCs). Major histocompatibility complex is coupled with the antigen and delivered to activated T and B cells on a dendritic cell.
Eosinophil	An immunological cell is called an eosinophil (leukocyte, or white blood cell). They contribute to the spread of infection or inflammation.
Granulocyte	When a pathogen attacks, granulocytes, which include eosinophils, neutrophils, and basophils, produce harmful substances such as enzymes, antimicrobial compounds, nitrogen oxides, and other proteins.
Human leukocyte antigens	The major histocompatibility complex in human form (MHC). More than 200 genes make up the MHC complex, which is divided into three classes: I, II, and III. Almost all cells' surfaces produce proteins that are produced by class I genes. Immune cells' outer surfaces include class II genes. Also connected to the immune system and inflammation are class III genes.
Natural killer (NK) cell	It is the body's earliest defense; the main effector cell of the innate immune system. Other cells send them activating and inhibiting signals.
T Lymphocyte	An immune-supporting white blood cell. The thymus is the site where cytotoxic, memory, helper, and regulatory T cells are developed.A patient's own T cells are used in CAR T-cell therapy to fight cancer.

Continued

Table 2.3 Immune system components glossary.—cont'd

Component	General description
	Cancer cells can be identified and combated in a lab by developing T cells with unique receptors (chimeric antigen receptors).
Cytotoxic T cell	Adaptive immunity is primarily mediated by T cells that are cytotoxic. A cytotoxic T cell that has been activated can penetrate nonlymphoid tissues as well as blood vessel walls. It is also possible for them to pass through the blood-brain barrier.
Memory T cell	A single memory T cell can produce several cytotoxic T cells. When activated cytotoxic T cells destroy the infection, memory T cells remain to prevent a recurrence.
Helper T cell	Helper T cells release cytokines that aid in the plasma cell differentiation of B cells. These cells also aid in the activation of macrophages and cytotoxic T cells.
Regulatory T cell	Tregs, also known as regulatory T cells, aid in immune system suppression.
Lymphocyte	Both lymphatic tissue and blood include immune cells known as lymphocytes. T and B lymphocytes are the two main subtype types.
Macrophage	Tissues include large white blood cells called macrophages, which are particularly good at engulfing and digesting infections, foreign objects, and cellular debris.
Mast cell	Mast cells produce histamine, which helps the body get rid of allergens.
Monocyte	The circulation contains enormous white blood cells that are skilled at absorbing and digesting pathogens, cellular waste, and other foreign substances. Monocytes can grow into macrophages.
Neutrophil	A granulocyte and phagocyte subtype of white blood cell that helps the body fight illness. By eating germs, neutrophils destroy them.

(Seiwert, 2019). Pathogens may be kept out of host cells and from infecting them thanks to antibody neutralization. The bacteria that have been neutralized by the antibody coating can subsequently be filtered by the spleen and excreted in the urine or feces. In a process known as opsonization, antibodies also label pathogens for phagocytic cells like neutrophils or macrophages to annihilate. Certain antibodies provide complement proteins with a spot to bind in a process known as complement fixation (Molnar & Gair, 2013).

Complement and antibodies work together to hasten the removal of infections. Active immunity, which refers to the host's active immunological response to an illness or a vaccine, is the creation of antibodies by plasma cells in response to an antigen (Tomar & De, 2014). In the passive immune response, antibodies that are not produced by the host's own plasma cells are presented to the host. For instance, the placenta allows circulating antibodies in a pregnant woman's body to reach the developing fetus. The presence of these antibodies benefits the infant for many months after delivery (Tomar & De, 2014).

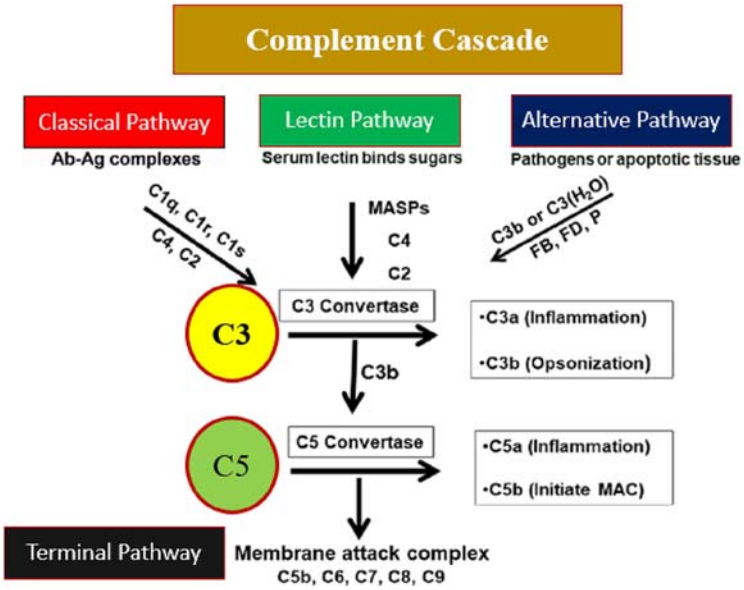

Fig. 2.4 The complement cascade the complement cascade.

7. Cell-mediated immune response

Immunity mediated by cells, also known as cellular immunity, does not rely on antibodies but rather on other immune cells to activate. When an antigen is presented, cell-mediated immunity activates phagocytes and antigen-specific cytotoxic T-lymphocytes, which destroy infected cells. Moreover, immune responses involve the release of cytokines, which play an important role in identifying infections. Phagocytes and cytokines assist T lymphocytes in detecting infections and responding appropriately, unlike B cells. By identifying and destroying the infected cells, these T lymphocytes help prevent infection from spreading. Pathogens are instead digested and split up into hundreds or thousands of antigens by dendritic cells and macrophages. An infection is identified, engulfed, and displayed by an antigen-presenting cell (APC), which then alerts the adaptive immune response. These APCs will take in phagocytose infections once they are identified (Molnar & Gair, 2013). After that, antigen fragments will reach the APC's surface, where they will act as a signal for further immune cells (McComb et al., 2019). The phagocytic vesicle joins an intracellular lysosome during macrophage phagocytosis (Weiss & Schaible, 2015). After the antigen is ready to be presented within the phagolysosome, the fragmented elements are next loaded onto MHC class II molecules and delivered to the cell surface. Before helper T cells can effectively react to an antigen, they need an MHC class II molecule to ingest and integrate it (Savina & Amigorena, 2007). In order to identify invaders, the MHC class II expressed on the surface of APCs assembles

complexes with foreign antigens. In response to an antigen assault, it does not require antibodies; instead, it activates phagocytes and cytotoxic T cells that are particular to the antigen Furuta and Roche (2015).

7.1 MHC (major histocompatibility complex)

Major histocompatibility complex (MHC) proteins play a key role in adapting immunity (Wieczorek et al., 2017). Three basic classes of membrane-bound glycoproteins are encoded by the MHC, which is a huge genetic complex with many loci. A variety of antigenic peptides are produced by the breakdown of antigen molecules, so instead of possessing specific selectivity for antigen characteristics, these molecules bind to them. MHC molecules of class I and class II have a cleft in which the antigenic peptide binds and is transmitted to T cells. Antigens are typically recognized by T-cytotoxic cells in combination with class I molecules, whereas antigens are generally recognized by T-helper cells in combination with class II molecules (Yewdell et al., 2001). There are substantial differences between these three classifications: (1) Class I gene products have the principal function of delivering peptide antigens to Tc cells; class I MHC genes encode glycoproteins that appear on nearly all nucleated cells' surfaces. A second class of MHC genes encode glycoproteins that are expressed predominantly on antigen-presenting cells (macrophages, dendritic cells, and B cells) and present antigenic peptides to T cells. The Class III MHC genes create components of the complement system and inflammatory chemicals, which are released in the body (Yewdell et al., 2001). MHC molecules of class I and class II are structurally similar and perform similar functions in antigen processing, another important factor. There is no significant difference between Class I and Class II of the major histocompatibility complex concerning folds. MHC class I binding platforms consist of one heavy-chain (HC), while MHC class II binding platforms consist of two chains (a -chain and a -chain) (Wieczorek et al., 2017). As a result of the two domains combining, a base has been formed with a slightly bent sheet and two -helices separated sufficiently to accommodate peptide chains. The peptide-binding unit is assisted by two immunoglobulins (Ig) domains proximal to the membrane. Beta-2 macroglobulin, the invariant light chain of MHC class I, forms the second Ig-type domain through noncovalent interactions. Wieczorek et al. (2017) report that the transmembrane helices bind both chains of MHC class II to the membrane (HCs of MHC class I and HCs of MHC class II).

8. Conclusion

Studying the immune system's cells and their functions is important for understanding how the body protects itself against viruses and other dangers. Each kind of immune cell in the body has a particular purpose, and the immune system is a complicated network of cells, tissues, and organs that work together to defend the body. Innate

and adaptive immunity both play crucial roles in defending the body from infections and other dangers, making them equally vital. The innate immune system, which comprises physical and chemical barriers like the skin and mucous membranes as well as white blood cells like neutrophils and macrophages, responds quickly and nonspecifically to infections and other dangers. This reaction serves as the body's initial line of defense against infections and has the potential to confine and get rid of viruses before they can do any damage. On the other hand, the adaptive immune system offers a more focused response that evolves over time when the body is exposed to various infections. T and B lymphocytes, specialized white blood cells that can identify and target certain antigens on infections, are involved in this response. These cells multiply and develop into effector cells when they come into contact with a pathogen, which they can use to neutralize the danger. The adaptive immune system also produces antibodies that have the ability to kill infections and stop them from doing damage. For the development of vaccines and therapies for infectious illnesses, as well as for understanding the underlying causes of immune-related disorders such as autoimmune diseases, allergies, and immunodeficiencies, it is essential to comprehend the actions of immune cells. Researching the immune system also has larger ramifications for areas like cancer biology, where immune cells are involved in tumor monitoring and eradication. We can create novel methods for preventing and treating a variety of illnesses by comprehending the processes underlying immunological dysfunction and the operation of the immune system. Hence, by examining immune system cells, scientists may be able to find indicators that may be used to anticipate how a person will react to particular treatments or diseases, resulting in individualized treatment choices.

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CHAPTER 3

Organ-specific autoimmune disorders

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1. Introduction to autoimmune disorders

Autoimmune disorders, commonly referred to as autoimmune illnesses, are a class of diseases in which the immune system of the body unintentionally targets its own healthy cells and tissues. The immune system's primary function is to defend the body against harmful diseases including bacteria, viruses, and other intruders. In autoimmune illnesses, however, the immune system degenerates and starts to attack healthy cells and tissues as though they were outside intruders. Numerous symptoms and health issues might result from this.

White blood cells, antibodies, and other immune system elements cooperate to recognize and eliminate dangerous chemicals in a healthy immune system. Self-recognition is impaired in autoimmune illnesses, and the immune system is unable to distinguish between "self" and "non-self." Over 80 autoimmune diseases are recognized, and they can affect almost any organ in the body. Rheumatoid arthritis, lupus, multiple sclerosis, type 1 diabetes, and celiac illness are a few typical instances (Wang et al., 2015). Although the precise origin of autoimmune illnesses is not entirely understood, it is thought that a complex interaction of hereditary and environmental variables is to blame. These disorders may be genetically predisposed in some people, and environmental factors like infections or exposure to specific chemicals may also contribute to the immune response.

The specific illness and the organs or tissues that are impacted can have a significant impact on the symptoms of autoimmune disorders. Fatigue, joint discomfort, muscular weakness, skin rashes, and digestive issues are a few typical symptoms. Over time, symptom severity can also change. Because autoimmune disorders' symptoms might resemble those of other diseases, diagnosing them can be difficult. To make a diagnosis, doctors frequently combine medical histories, physical examinations, blood testing, and imaging studies. A biopsy of the afflicted tissue may be required in some circumstances (Bieber et al., 2023). Although there is no known treatment for autoimmune illnesses, many can be controlled. Typically, the purpose of treatment is to decrease inflammation and

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to inhibit the aberrant immune response. Corticosteroids, immunosuppressants, and disease-modifying antirheumatic medicines (DMARDs) are often prescribed medications. Additionally, lifestyle adjustments like stress management and nutritional changes could be advised.

1.1 What are autoimmune disorders?

The term "autoimmune disorder" refers to a group of diseases where the body's immune system, which is meant to protect against pathogens like bacteria and viruses, mistakenly targets and attacks its own healthy cells, tissues, and organs. Autoimmune disorders are a subset of these diseases. In essence, the immune system becomes unable to differentiate between "self" and "non-self," which causes tissue damage, inflammation, and a variety of symptoms and health issues that are unique to the affected organs or systems. There are approximately 80 identified autoimmune illnesses, each with a distinct set of symptoms and effects that can affect almost any organ of the body (Mackay et al., 2001). These conditions can be chronic and require ongoing management, as there is typically no cure, but various treatments are available to help control symptoms and reduce the autoimmune response.

1.2 Immune system malfunction-leading to self-attack

The immune system is a complex network of cells and proteins designed to protect the body from harmful invaders like bacteria, viruses, and other pathogens. It has a built-in mechanism for recognizing and distinguishing between the body's own healthy cells and foreign substances (Ahsan, 2017; Wasniewska & Bossowski, 2021). However, in autoimmune disorders, this system malfunctions, leading to a self-attack. Here's a brief explanation of how this malfunction occurs.

- **Loss of Self-Tolerance:** The immune system has a crucial feature called "self-tolerance." This means it can recognize the body's own cells and tissues as "self" and not mount an immune response against them. This self-recognition is essential to prevent the immune system from attacking healthy tissues.
- **Triggering Event:** In autoimmune disorders, there is often an initial triggering event, although it's not always clear what causes it. This trigger can be an infection, exposure to certain chemicals, or a combination of genetic and environmental factors. This event somehow confuses or "breaks" the immune system's self-recognition process.
- **Production of Autoantibodies:** As a result of this confusion, the immune system starts to produce autoantibodies. Autoantibodies are antibodies that mistakenly target the body's own cells and tissues as if they were foreign invaders. These autoantibodies can initiate inflammation and damage to the healthy cells.
- **Cellular Attack:** In addition to autoantibodies, certain immune cells, such as T cells, can become activated and directly attack healthy cells and tissues. This immune

response leads to inflammation, tissue damage, and the characteristic symptoms of autoimmune diseases.

- **Specificity:** Autoimmune disorders are highly specific to the type of cells or tissues that are targeted. For example, in rheumatoid arthritis, the immune system attacks the joints, while in multiple sclerosis, it attacks the protective covering of nerve fibers in the central nervous system.

1.3 Organ-specific and systemic autoimmune disorders

Autoimmune disorders can be broadly categorized into two main types based on their scope and the areas of the body they affect: organ-specific autoimmune disorders and systemic autoimmune disorders (Ramos-Casals et al., 2021). Here is a distinction between the two.

1.3.1 Organ-specific autoimmune disorders

Organ-specific autoimmune disorders primarily target and affect a specific organ or tissue in the body. The immune response is localized to a particular site. Examples includes

- **Type 1 Diabetes:** The immune system attacks the insulin-producing cells in the pancreas, affecting blood sugar regulation.
- **Hashimoto's Thyroiditis:** The immune system targets the thyroid gland, leading to hypothyroidism.
- **Celiac Disease:** The immune system reacts to gluten, primarily affecting the lining of the small intestine.

Symptoms in organ-specific autoimmune disorders are typically related to the specific organ or tissue under attack. For instance, in Type 1 Diabetes, symptoms include increased thirst, frequent urination, and high blood sugar levels. Similarly, diagnosis often involves tests specific to the affected organ or tissue. Treatment may focus on managing symptoms, replacing missing hormones, or controlling the immune response in that particular area.

1.4 Systemic autoimmune disorders

Systemic autoimmune disorders affect multiple organs and systems throughout the body. The immune response is not confined to a single organ or tissue but is distributed systemically. Examples includes

- **Systemic Lupus Erythematosus (SLE):** SLE can affect the skin, joints, kidneys, heart, lungs, and other organs.
- **Rheumatoid Arthritis:** Although it primarily affects the joints, it can also have systemic effects on the heart, lungs, and other organs.
- **Sjögren's Syndrome:** These affects the salivary and tear glands, but it can also involve other parts of the body, including joints and nerves.

Symptoms associated with systemic autoimmune disorders are diverse and can involve a wide range of organs and tissues. Common systemic symptoms may include fatigue, joint pain, skin rashes, and fever. Diagnosis often relies on a combination of symptoms, blood tests, and medical history. Treatment aims to manage the overall immune response and alleviate symptoms affecting various parts of the body. Medications that modulate the immune system are commonly used. This chapter aims to provide a scholarly and in-depth exploration of organ-specific autoimmune disorders, delving into the intricate mechanisms, diagnostic methodologies, and therapeutic strategies employed in managing these conditions. By focusing on the autoimmune afflictions that selectively target particular organs—such as the skin (e.g., psoriasis), thyroid (e.g., Hashimoto's thyroiditis), pancreas (e.g., type 1 diabetes), and joints (e.g., rheumatoid arthritis)—we will uncover the nuances of these disorders at a molecular and clinical level. Whether one's interest is driven by a clinical perspective, a scientific inquiry, or the personal experience of living with or caring for individuals afflicted by these disorders, this exploration strives to provide a comprehensive understanding of the complexities inherent in organ-specific autoimmune diseases.

2. Immunological basis of organ-specific autoimmune disorders

Organ-specific autoimmune diseases affect specific organs of the body where the target autoantigen is located. Aberrant B cell and T cell reactivity to the self-antigen triggers autoimmunity. Although autoreactive T cells play the decisive role in the process, autoantibodies are more prominently manifested (Pisetsky, 2023).

2.1 Role of autoantibodies and autoreactive T cells

There is a minimal level of autoantibodies present even in healthy individuals, which, under normal conditions does not cause any autoimmunity and are referred to as the natural autoantibodies (Pisetsky, 2023). Natural autoantibodies are mainly IgM. There exists another type of autoantibodies which cause pathological manifestations. These are mostly high-affinity, somatically mutated IgG autoantibodies and are referred to as pathogenic autoantibodies. They are rarely IgA (e.g., in autoimmune intestinal disease) or IgM (e.g., in autoimmune hemolyticanemia) (WSß et al., 2011).

Pathogenic autoantibodies contribute to various immune-mediated diseases. The association between autoantibodies and tissue pathology tends to be more obvious in the context of organ-specific autoimmune diseases than in systemic autoimmune diseases. Autoantibodies induce Organ-specific Autoimmune Disorders through a multitude of pathophysiological pathways including mimicking hormone stimulation of receptor (Graves' disease), blocking neural transmission by receptor blockade or alteration of the synaptic structures (myasthenia gravis), induction of altered signaling (antibodies against desmoglein-3 in pemphigus), triggering uncontrolled microthrombosis

(autoantibodies against ADAMTS13 in acquired thrombotic thrombopenic purpura), cell lysis (idiopathic thrombocytopenia) (Yurttutan et al., 2018).

Like autoantibodies, autoreactive T cells also exist in a healthy individual. In the context of autoimmune disease, antigen-specific $CD4^+$ T helper cells (TH) cells can stimulate autoantibody production by B cells whereas cytotoxic $CD8^+$ T cells can damage or kill cells (Tsai et al., 2020). Patients with T cell defects can present with a variety of organ specific autoimmune diseases (e.g., type 1 diabetes mellitus in infancy, hypothyroidism, and Addison's disease) (Mackay et al., 2001). The autoreactive T-cell precursor level in the target tissue is much higher than in circulation. Autoreactive cytotoxic T lymphocytes recognize a target cell by binding the T-cell receptor (TCR) to the appropriate combination of MHC I and autoantigen-derived peptides. Then, a complex of MHC I and auto antigen derived peptides directly kills target cells through different mechanisms: (i) secretion of cytotoxic granules (perforin and granzyme B)resulting in disintegration of the cell membrane and induced apoptosis; (ii) activation of Fas—Fasligand, which induces apoptosis; and (iii) release of cytokines (such as TNF-and interferon-c), leading to tissue injury (Mackay et al., 2001; Wang et al., 2015).

2.2 Mechanism triggering loss of self-tolerance

Even under the strictest control by central and peripheral tolerance, a small number of autoreactive T and B cells "leak out" into the periphery in normal individuals. However, they will remain harmless unless there is a genetic predisposition to break tolerance and an environment trigger or triggers (Wang et al., 2015).

The primary drivers of autoimmune disorders are $CD4^+$ T-lymphocytes, which modify the responses of other immune cells. $CD4^+$ T cell activation is a coordinated process that requires three distinct signals: Signal 1, which is mediated by antigen recognition on MHC-II molecules; Signal 2, which boosts signal 1 in a costimulatory manner; and Signal 3, which helps to differentiate the activated cells into functionally relevant subsets. These signals are disrupted during autoimmunity and prompt $CD4^+$ T cells to break tolerance (Krovi & Kuchroo, 2022). Common mechanisms for losing self-tolerance include reduced deletion or enhanced activation of autoreactive $CD4^+$ T-helper (Th) lymphocytes, defective immunomodulation by $CD4^+$ regulatory (Treg) and $CD8^+$ suppressor (Ts) T-lymphocytes, dysregulated signaling (leading to a relative increase in pro-inflammatory cytokines), comparable structure between self-antigens and foreign molecules, or expression of new epitopes on previously hidden or xenobiotic-modified self-proteins (Wang et al., 2015). Organ-specific autoimmune disorder is mainly a Th1 or Th17 mediated process. Th1 and Th17 cells help recruit and stimulate other immune effector elements. This role is normally counterbalanced by the opposing activity of $CD4^+$ Treg cells, a reduction in the numbers and/or function of Treg cells removes the check on potential immune reaction against one's self.

2.3 Genetic and environmental factors contributing to susceptibility

Predisposing factors for autoimmune diseases include genetic background, hormonal status, pathogens, and xenobiotic exposures (Wang et al., 2015). The current model of autoimmune disease suggests that disease develops in a genetically susceptible individual in response to an environmental trigger (Pisetsky, 2023). Multiple genes with specific gene mutations (i.e., AIRE, TNFRSF6, FOXP3 and CD25), HLA susceptible, non-HLA loci (i.e., PRPN22, IRF5-TNFO3 and BACH2) as well as epigenetic mechanisms (methylation, acetylation, ubiquination, sumoylation, phosphorylation and microRNA) have been implicated in specific autoimmune diseases (Wang et al., 2015). Most autoimmune diseases are multigenic; nevertheless single-gene mutations can powerfully influence disease susceptibility. Heterozygous mutations in AIRE cause organ-specific autoimmune disease (Oftedal et al., 2015). Many autoimmune diseases occur with a higher frequency in women than men, with sex representing a major genetic risk factor.

Multiple environmental factors including microorganisms, xenobiotics (drugs, smoking, UV lights, heavy metals), host microbiota and nutrition have been implicated in the development of autoimmunity. "Molecular mimicry" is the most common mechanism that activates autoreactive T and B cells. "Epitope spreading" is a mechanism that results in generation of multiple neo-epitopes. In addition, by modulating innate and adaptive immunity, the microbiota and nutrition (e.g., vitamin D, iodine and gluten) may also contribute to loss of tolerance (Wang et al., 2015).

3. Endocrine organ-specific autoimmune disorders

The human endocrine system, consisting of a complex network of glands and organs, plays a pivotal role in maintaining homeostasis within the body. These endocrine organs secrete hormones, which act as messengers, regulating a myriad of physiological processes, from metabolism to growth and development, and even the immune response. This intricate system is finely tuned to ensure that hormones are released in the right amounts at precisely the right time. However, this harmony can be disrupted when the immune system malfunctions, leading endocrine organ-specific autoimmune disorders. Endocrine organ-specific autoimmune disorders are characterized by the immune system's attack on a particular endocrine organ or gland, disrupting its normal function and causing a range of clinical symptoms.

We will explore how autoimmune responses can affect organs such as the thyroid, pancreas, and adrenal glands. Understanding the underlying mechanisms and complexities of these disorders is crucial not only for healthcare professionals but also for patients who grapple with the profound impact these conditions have on their daily lives. This section will focus on several well-documented endocrine organ-specific autoimmune disorders, including type 1 diabetes mellitus (McLeod & Cooper, 2012), Hashimoto's

thyroiditis (Pociot & Lernmark, 2016), and Addison's disease (Michels & Eisenbarth, 2009). These conditions represent a diverse spectrum of endocrine disorders, each with its unique etiology, clinical presentation, and therapeutic approach.

3.1 Type 1 diabetes: Autoimmunity against pancreatic β-cells

Type 1 Diabetes (T1D) is a classic example of an endocrine organ-specific autoimmune disorder, characterized by the immune system's attack on the insulin-producing β-cells of the pancreas. This immune assault leads to a lack of insulin production and subsequent hyperglycemia, which is the hallmark of diabetes.

The precise etiology of T1D remains complex and multifactorial. Genetic susceptibility plays a crucial role, with specific human leukocyte antigen (HLA) alleles contributing to increased risk. Environmental factors, such as viral infections, may trigger the autoimmune response.

Research has identified various autoantibodies associated with T1D, including those targeting insulin, GAD65, IA-2, and ZnT8. These autoantibodies serve as diagnostic markers and are indicative of the immune attack on pancreatic β-cells.

Promising therapeutic approaches, such as immunomodulation and beta-cell replacement, are under investigation to halt the immune response and restore insulin production. Additionally, researchers are exploring ways to predict and prevent T1D, furthering our understanding of this autoimmune disorder (Pociot & Lernmark, 2016).

3.2 Hashimoto's thyroiditis: Autoimmunity against thyroid gland

Hashimoto's Thyroiditis, an autoimmune disorder, primarily targets the thyroid gland. In this condition, the immune system mistakenly recognizes thyroid proteins as foreign invaders, initiating an inflammatory response. Over time, the thyroid gland becomes infiltrated with immune cells, resulting in hypothyroidism.

Antithyroid antibodies, such as thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb), are commonly detected in patients with Hashimoto's Thyroiditis. These antibodies are indicative of the autoimmune process and contribute to the destruction of thyroid tissue.

Genetic predisposition plays a role in the development of Hashimoto's Thyroiditis, as certain HLA alleles have been linked to increased susceptibility. Additionally, environmental factors, such as iodine intake and viral infections, can trigger or exacerbate the condition (McLeod & Cooper, 2012).

Treatment typically involves thyroid hormone replacement therapy to restore normal thyroid function. While this approach does not target the underlying autoimmune response, it effectively manages the hypothyroidism associated with Hashimoto's Thyroiditis.

3.3 Addison's disease: Autoimmunity against adrenal cortex

Addison's Disease, or primary adrenal insufficiency, is another endocrine organ-specific autoimmune disorder. In this condition, the adrenal cortex is targeted by the immune system, leading to the destruction of the adrenal glands and reduced production of cortisol and aldosterone.

Autoantibodies, such as 21-hydroxylase antibodies, are commonly found in patients with Addison's Disease and are indicative of the autoimmune nature of the disorder.

Genetic factors play a role in predisposition to Addison's Disease, with certain HLA alleles being associated with increased susceptibility. Autoimmune polyendocrine syndrome type 1 (APS-1) and type 2 (APS-2) are conditions that may include Addison's Disease and provide further insight into the genetic and immunological basis of this disorder (Michels & Eisenbarth, 2009).

The primary treatment for Addison's Disease involves lifelong hormone replacement therapy to replace the deficient cortisol and aldosterone. Without treatment, this condition can be life-threatening.

4. Neurological organ-specific autoimmune disorders

Neurological organ-specific autoimmune disorders are a group of conditions where the immune system, mistakenly attacks specific components of the nervous system. These disorders can have a profound impact on the affected individuals, causing a wide range of neurological symptoms. We will explore three most prominent neurological organ-specific autoimmune disorders: Multiple Sclerosis, Myasthenia Gravis, and Autoimmune Encephalitis. Each disorder results from autoimmunity against different components of the nervous system, leading to unique clinical manifestations and diagnostic challenges.

4.1 Multiple sclerosis: Autoimmunity targeting myelin sheath

Multiple Sclerosis (MS) is a chronic autoimmune disease characterized by the immune system's attack on the myelin sheath, the protective covering of nerve fibers in the central nervous system (CNS). MS primarily affects the brain and spinal cord, disrupting the normal flow of electrical impulses and causing a wide array of neurological symptoms.

The exact cause of MS remains elusive, but it is believed to result from a combination of genetic predisposition and environmental factors. Specific genetic markers, such as the HLA-DR15 allele, have been associated with an increased risk of developing MS (Sawcer et al., 2011). Environmental factors, including viral infections and low vitamin D levels, are thought to contribute to the disease's development.

MS has a diverse clinical presentation, with symptoms varying widely from person to person. Common manifestations include fatigue, muscle weakness, coordination problems, visual disturbances, and cognitive impairment. MS often follows a relapsing-

remitting course, where symptoms come and go, but it can also transition to a progressive form as the disease advances.

Treatment for MS typically includes disease-modifying medications to reduce the frequency and severity of relapses, as well as symptom management with physical therapy, corticosteroids during relapses, and lifestyle adjustments.

4.2 Myasthenia gravis: Autoimmunity against the neuromuscular junction

Myasthenia Gravis (MG) is an autoimmune disorder that targets the neuromuscular junction, where nerve impulses connect with muscle cells. This condition results in muscle weakness and fatigue, especially with repetitive movements.

MG is primarily driven by autoantibodies that interfere with the normal function of acetylcholine receptors at the neuromuscular junction (Koneczny et al., 2019). The thymus gland plays a significant role in the development of MG, with thymic abnormalities found in many patients.

The hallmark of MG is muscle weakness that worsens with activity and improves with rest. This can affect various muscle groups, including those involved in eye movement, swallowing, and limb control. Ocular symptoms, such as ptosis (drooping eyelids) and diplopia (double vision), are common initial complaints.

Treatment involves medications that enhance neuromuscular transmission, such as acetylcholinesterase inhibitors and immunosuppressants. In some cases, thymectomy (removal of the thymus gland) may be recommended.

4.3 Autoimmune encephalitis: Inflammation of brain tissue due to autoimmune response

Autoimmune Encephalitis is a group of disorders characterized by inflammation of the brain tissue due to an autoimmune response. Unlike some other neurological autoimmune disorders that primarily affect the peripheral nervous system, autoimmune encephalitis involves inflammation within the brain itself.

Autoimmune encephalitis often results from antibodies targeting specific neuronal surface or synaptic proteins, leading to various clinical presentations (Ropper et al., 2018). Different antibodies are associated with distinct forms of autoimmune encephalitis, such as anti-NMDA receptor encephalitis and anti-LGI1 encephalitis.

The clinical manifestations of autoimmune encephalitis can be highly variable, depending on the specific antibodies involved. Common symptoms include altered mental status, psychiatric symptoms, seizures, and movement disorders.

Diagnosing autoimmune encephalitis typically requires clinical evaluation, neuroimaging, and cerebrospinal fluid analysis to detect signs of inflammation. Testing for specific autoantibodies associated with autoimmune encephalitis is also crucial for accurate diagnosis (Zuliani et al., 2012). Treatment includes high-dose corticosteroids and other

immunosuppressive medications to reduce the autoimmune response. Intravenous immunoglobulin (IVIG) and plasma exchange may also be used in severe cases.

5. Gastrointestinal organ-specific autoimmune disorders

Gastrointestinal organ-specific autoimmune disorders are a group of conditions characterized by the immune system's misguided attack on the tissues of the gastrointestinal system. These disorders often result in chronic inflammation and damage to specific parts of the digestive tract. We will delve into three prominent gastrointestinal organ-specific autoimmune disorders: Celiac Disease, Autoimmune Hepatitis, and the subtypes of Inflammatory Bowel Disease (IBD), namely Crohn's Disease and Ulcerative Colitis.

5.1 Celiac disease: Autoimmunity affecting small intestine due to gluten

Celiac Disease is an autoimmune disorder in which the ingestion of gluten triggers an immune response against the small intestine's lining. This immune response is primarily driven by the presence of tissue transglutaminase antibodies (tTG-IgA) and anti-endomysial antibodies (EMA-IgA). Genetic predisposition plays a significant role, with specific human leukocyte antigen (HLA) genotypes, particularly HLA-DQ2 and HLA-DQ8, associated with an increased risk (Rubio-Tapia et al., 2009).

The clinical presentation of Celiac Disease is highly variable, with symptoms ranging from mild to severe. Common manifestations include diarrhea, abdominal pain, bloating, fatigue, and weight loss. Celiac Disease can also manifest with extra-intestinal symptoms, affecting various organ systems. It is crucial to note that strict adherence to a gluten-free diet is the cornerstone of managing Celiac Disease (Ludvigsson et al., 2014).

Management primarily involves a strict gluten-free diet, avoiding all sources of gluten. This dietary change helps control symptoms and prevents long-term complications.

5.2 Autoimmune hepatitis: Inflammation of liver tissue due to autoimmune attack

Autoimmune Hepatitis is a chronic inflammatory liver disease characterized by autoimmunity against hepatic antigens. While the exact cause remains unknown, it is believed that genetic predisposition, along with environmental triggers, contributes to disease development (Liberal et al., 2013). Specific autoantibodies, including anti-smooth muscle antibodies (SMA) and anti-liver/kidney microsomal antibodies (LKM-1), are often present in patients with autoimmune hepatitis.

Autoimmune Hepatitis can present with a wide range of clinical symptoms, such as fatigue, jaundice, hepatomegaly, and pruritus. Left untreated, it can lead to cirrhosis and liver failure. It is crucial to differentiate autoimmune hepatitis from other forms of hepatitis to ensure proper management.

Diagnosing autoimmune hepatitis typically involves serological tests to detect specific autoantibodies and the evaluation of liver function. Liver biopsy may be necessary to confirm the diagnosis and assess the degree of liver damage (Manns et al., 2010). Treatment consists of immunosuppressive medications, such as corticosteroids and azathioprine, to reduce liver inflammation. Liver transplantation may be considered in severe cases.

5.3 Inflammatory Bowel Disease (IBD) subtypes: Crohn's Disease and Ulcerative Colitis

Inflammatory Bowel Disease is a complex group of autoimmune disorders that primarily affect the gastrointestinal tract. While the exact cause is not fully understood, it is thought to result from a combination of genetic predisposition and environmental factors. Specific genetic markers, such as NOD2 and IL23R, have been associated with an increased risk of IBD (Khor et al., 2011).

Crohn's Disease can affect any part of the digestive tract, from the mouth to the anus. Common symptoms include abdominal pain, diarrhea, weight loss, and fatigue. It often leads to inflammation that can penetrate the entire bowel wall and form strictures and fistulas (Torres et al., 2017).

Ulcerative Colitis primarily affects the colon and rectum. Symptoms include bloody diarrhea, abdominal pain, urgency, and tenesmus. In severe cases, it can lead to toxic megacolon and an increased risk of colorectal cancer (Ungaro et al., 2017). Medications such as anti-inflammatory drugs, immunosuppressants, and biologics are used to manage IBD symptoms. Dietary modifications and lifestyle changes may also be recommended.

6. Skin and connective tissue organ-specific autoimmune disorders

Skin and connective tissue organ-specific autoimmune disorders encompass a diverse group of conditions where the immune system mistakenly targets and attacks components of the skin and connective tissues. These disorders often lead to chronic inflammation, tissue damage, and a variety of cutaneous and systemic symptoms. In this section, we have discussed three major skin and connective tissue organ-specific autoimmune disorders: Psoriasis, Vitiligo, and Systemic Sclerosis (Scleroderma). Each disorder has distinct characteristics, etiology, and clinical presentations, but they share the common theme of autoimmunity affecting the skin and connective tissues.

6.1 Psoriasis: Chronic skin disorder with autoimmune components

Psoriasis is a chronic autoimmune skin disorder characterized by the hyperproliferation of keratinocytes in the epidermis. While its exact cause remains incompletely understood, it is thought to result from a combination of genetic predisposition and environmental triggers (Nestle et al., 2009). Specific genetic markers, such as HLA-Cw6, have been associated with an increased risk of psoriasis.

Psoriasis typically presents with well-defined, red, raised patches of skin covered with silvery scales. The most common form is plaque psoriasis, which can affect any part of the body, including the scalp, elbows, knees, and lower back. Psoriasis can lead to itching, discomfort, and significant psychosocial impact (Griffiths et al., 2007).

Diagnosing psoriasis often involves clinical evaluation, including a physical examination of the affected skin. In some cases, a skin biopsy may be performed to confirm the diagnosis. While psoriasis is primarily a clinical diagnosis, certain laboratory tests can help exclude other skin conditions (W.B. Kim et al., 2017). Treatment options include topical creams, phototherapy, and systemic medications (like immunosuppressants or biologics) to control skin inflammation and alleviate symptoms.

6.2 Vitiligo: Autoimmune destruction of melanocytes

Vitiligo is an autoimmune skin disorder characterized by the progressive loss of melanocytes, the cells responsible for skin pigmentation. The precise cause of vitiligo is not fully understood, but autoimmunity is believed to play a significant role. Genetic factors and environmental triggers, such as oxidative stress, have been implicated in the development of the condition (Spritz & Andersen, 2017; Xuan et al., 2022).

Vitiligo presents with depigmented, white patches of skin that can appear anywhere on the body. These patches may gradually enlarge and can affect hair and mucous membranes. Vitiligo does not typically cause physical discomfort, but it can have a significant impact on a person's self-esteem and body image (Ezzedine et al., 2015).

Diagnosing vitiligo is primarily clinical, as the characteristic appearance of depigmented patches is often sufficient. In some cases, a Wood's lamp examination may be used to highlight areas of depigmentation. Laboratory tests are occasionally performed to rule out other conditions (Taïeb & Picardo, 2009). Therapies for vitiligo include topical corticosteroids, topical calcineurin inhibitors (CNIs), narrowband UVB phototherapy, and in some cases, surgical procedures like skin grafting or tattooing.

6.3 Systemic sclerosis (scleroderma): Involvement of skin and connective tissues

Systemic Sclerosis, commonly referred to as scleroderma, is an autoimmune disorder that affects the skin and connective tissues. The exact cause of scleroderma is not fully understood, but it is believed to result from a combination of genetic and environmental factors. Autoimmunity, especially the production of autoantibodies, plays a central role in the disease (Gabrielli et al., 2009).

Scleroderma can have two main forms: localized and systemic. In localized scleroderma, the condition primarily affects the skin, resulting in thickened and hardened patches. Systemic sclerosis, on the other hand, can involve not only the skin but also internal organs, leading to a range of symptoms, including Raynaud's phenomenon, skin thickening, joint pain, and potential organ involvement, such as the lungs and gastrointestinal tract (Denton & Khanna, 2017).

Diagnosing scleroderma typically involves a combination of clinical evaluation, serological tests to detect autoantibodies, skin biopsies, and imaging studies. Identifying the extent of skin and internal organ involvement is crucial for determining the appropriate management (Xuan et al., 2022). Management involves symptom-specific treatment, such as medications to control organ involvement and complications. Immunosuppressive drugs may be used for skin and lung involvement. Physical therapy and lifestyle adjustments are also crucial.

7. Respiratory and ocular organ-specific autoimmune disorders

Respiratory and ocular organ-specific autoimmune disorders are a subset of autoimmune diseases that primarily target specific organs within the respiratory and ocular systems. These disorders primarily affect specific organs within the respiratory and ocular systems, they can also have systemic effects, and patients may experience symptoms beyond the targeted organs. Proper diagnosis and management typically involve a combination of medical history, clinical evaluation, and specialized tests to determine the extent of organ involvement. Treatment often focuses on controlling inflammation and managing symptoms to improve the patient's quality of life and preserve organ function.

7.1 Respiratory organ-specific autoimmune disorders

Respiratory organ-specific autoimmune disorders are conditions in which the immune system mistakenly targets and attacks specific components of the respiratory system, leading to inflammation and damage to these organs or tissues. Here are some examples of respiratory organ-specific autoimmune disorders

- **Goodpasture's Syndrome:** This rare autoimmune disorder primarily affects the lungs and kidneys. The immune system produces antibodies that attack the basement membrane of the lungs and glomeruli in the kidneys, leading to lung bleeding and kidney damage (Fernandes et al., 2016). Symptoms include coughing up blood, difficulty in breathing, and kidney dysfunction.
- **Eosinophilic Granulomatosis with Polyangiitis (EGPA):** EGPA is a type of vasculitis that affects small and medium-sized blood vessels. It can cause inflammation in the airways and lungs, leading to asthma-like symptoms and lung damage (Karadeniz & Tufan, 2021). Other symptoms include cough, wheezing, and systemic symptoms like fever and fatigue.

7.2 Ocular organ-specific autoimmune disorders

Ocular organ-specific autoimmune disorders are conditions in which the immune system mistakenly targets and attacks the tissues of the eye, leading to inflammation, damage, and a range of ocular symptoms. Major examples of the same include.

7.2.1 Autoimmune uveitis

Uveitis is an inflammatory condition that affects the uvea (middle layer of the eye). The uvea consists of the iris (colored part of the eye), the ciliary body (which produces the eye's aqueous humor), and the choroid (a layer of blood vessels that nourishes the retina). In autoimmune uveitis, the immune system mistakenly targets and attacks the tissues of the uvea as if they were foreign invaders.

The exact cause of autoimmune uveitis is not always clear, but it is believed to involve a combination of genetic predisposition and environmental factors. Certain autoimmune diseases, such as rheumatoid arthritis and ankylosing spondylitis, are associated with an increased risk of developing uveitis (García-Aparicio et al., 2021). Symptoms includes eye redness, pain or discomfort, sensitivity to light (photophobia), floaters, which are tiny specks or spots in the field of vision and vision changes or loss of complete vision (Plekhanov et al., 2019).

Diagnosis of autoimmune uveitis involves a comprehensive eye examination by an ophthalmologist. Additional tests may be necessary to determine the underlying cause and the severity of the inflammation. Treatment of autoimmune uveitis typically involves addressing the inflammation and managing the underlying autoimmune condition if one is present. General treatment options may include,

- Steroid eye drops or injections to reduce inflammation.
- Immunosuppressive medications to control the immune response.
- Treating any underlying autoimmune disease.
- Monitoring by an eye specialist to assess progress and adjust treatment as needed.

Early diagnosis and prompt treatment are essential to prevent vision loss and manage the inflammation associated with autoimmune uveitis effectively. People with autoimmune uveitis often require ongoing care to manage the condition and minimize the risk of recurrent inflammation and complications.

7.2.2 Graves' disease: Autoimmunity targeting thyroid and eye tissues

Graves' disease, an autoimmune disorder that affects the thyroid gland, can also lead to eye problems (affects eye muscles and tissues). The autoimmune aspects of Graves' disease involve the immune system mistakenly attacking these tissues.

7.2.2.1 Thyroid gland involvement

It is the most common cause of hyperthyroidism, a condition in which the thyroid gland becomes overactive and produces too much thyroid hormone (Davies et al., 2020). In Graves' disease, the immune system produces antibodies known as thyroid-stimulating immunoglobulins or thyroid-stimulating antibodies (TSIs). These antibodies mimic the action of thyroid-stimulating hormone (TSH), a natural hormone that regulates thyroid function. TSIs attach to receptors on the thyroid gland's surface and stimulate it to produce excess thyroid hormones (triiodothyronine or T3 and thyroxine or T4). This leads

to hyperthyroidism, which can cause symptoms such as rapid heart rate, weight loss, anxiety, and heat intolerance.

7.2.2.2 Ocular involvement (Graves' ophthalmopathy or thyroid eye disease)

It causes inflammation and swelling of the eye muscles and tissues, resulting in bulging eyes and other eye-related issues (Wagner et al., 2022). The exact cause of this immune response is not fully understood, generally autoimmune response in Graves' ophthalmopathy involves inflammation, swelling of the eye muscles and tissues, and an accumulation of immune cells behind the eyes. This can lead to the characteristic eye changes seen in the condition. In some individuals with Graves' disease, the immune system also attacks the tissues surrounding the eyes, leading to a condition called Graves' ophthalmopathy or thyroid eye disease (TED).

Major symptoms include a range of eye-related symptoms, including bulging eyes (exophthalmos), redness, puffiness, eye pain, dryness double vision, and in severe cases, vision loss.

Treatment of Graves' ophthalmopathy may include addressing inflammation with medications like corticosteroids, managing eye symptoms, and, in some cases, surgical interventions to correct severe eye protrusion or double vision.

7.3 Allergic rhinitis and asthma: Autoimmune aspects of respiratory disorders

Allergic rhinitis and asthma are respiratory disorders that have allergic and immunological components, but they are not typically considered autoimmune disorders. However, they share some similarities with autoimmune diseases in terms of immune system involvement, they have distinct mechanisms and triggers. Autoimmune disorders involve the immune system mistakenly targeting the body's own tissues, whereas allergic rhinitis and asthma involve immune responses triggered by external allergens or irritants.

7.3.1 Allergic rhinitis

Allergic rhinitis, commonly known as hay fever, is an allergic response to allergens such as pollen, dust mites, pet dander, and mold spores (Bousquet et al., 2020; Varshney & Varshney, 2015). While it is not an autoimmune disorder, in this situation the immune system overreacts to harmless substances, perceiving them as threats. This triggers an immune response that includes the release of histamines and other chemicals, leading to symptoms like sneezing, runny nose, and itchy eyes.

Individuals with allergic rhinitis often have high levels of IgE antibodies, which play a key role in allergic reactions. IgE antibodies bind to allergens and trigger the release of histamine, causing allergy symptoms. Specific types of T-helper cells, such as Th2 cells, are involved in promoting the allergic response in allergic rhinitis. These cells release cytokines that contribute to inflammation and allergy symptoms.

7.3.2 Asthma

Asthma is a chronic respiratory condition characterized by inflammation and narrowing of the airways. While asthma is not an autoimmune disorder (Mukherjee & Nair, 2018), in asthma, the immune system responds to triggers like allergens, respiratory infections, or irritants by causing inflammation in the airways. This inflammation can lead to bronchoconstriction (narrowing of the airways) and the classic asthma symptoms of wheezing, coughing, and shortness of breath.

Eosinophils are a type of white blood cell that plays a role in the immune response to allergens. Elevated levels of eosinophils in the airways are common in allergic asthma, suggesting an allergic component to this subtype of asthma. IgE antibodies, which are involved in allergic responses, can also play a role in allergic asthma. When allergens trigger the release of IgE antibodies in the airways, it can lead to asthma exacerbations.

8. Diagnostic approaches and biomarkers

Diagnosing autoimmune diseases can be challenging due to their diverse range of symptoms and the overlap with other conditions. Skilled clinicians assess a patient's medical history, symptoms, and physical examination findings. The presence of characteristic symptoms, such as joint pain, rash, fatigue, and inflammation, can provide important diagnostic clues. However advanced diagnostic approaches often involve a combination of clinical evaluation, laboratory tests, imaging studies, and sometimes, tissue biopsies. Recently, biomarkers added the diagnostics of autoimmune disorder by monitoring disease progression, and predicting treatment response in autoimmune diseases (Fenton & Pedersen, 2023). Here's an overview of diagnostic approaches and biomarkers used in autoimmunity.

8.1 Immunological and serological laboratory tests for diagnosis

Immunological and serological tests play a critical role in the diagnosis of autoimmune diseases. These tests help identify specific antibodies, immune system abnormalities, and markers of inflammation or tissue damage associated with autoimmune conditions (Sciascia et al., 2023). Here are some common immunological and serological tests used for diagnosing autoimmunity.

- **Rheumatoid Factor (RF):** RF is an antibody often elevated in rheumatoid arthritis but can also be present in other autoimmune conditions.
- **Complement Levels:** Measurement of complement components (C3 and C4) can provide information about complement activation, which is often altered in autoimmune diseases like SLE.
- **Immunoglobulin Levels:** Abnormal levels of immunoglobulins (IgG, IgA, IgM) may indicate immune system dysfunction.

- **Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP):** These tests measure markers of inflammation and are often elevated in autoimmune diseases with an inflammatory component.
- **Cytokine Profiling:** Analysis of cytokine levels in the blood can help assess the immune response and the involvement of specific cytokines in autoimmune diseases.
- **HLA Typing:** Human leukocyte antigen (HLA) typing can identify genetic markers associated with an increased risk of developing certain autoimmune diseases, such as HLA-B27 in ankylosing spondylitis.
- **Specific Organ Function Tests:** Depending on the suspected autoimmune disease, tests such as liver function tests, kidney function tests, thyroid function tests, and others may be performed to evaluate the involvement of specific organs.
- **Immunofluorescence Assays:** These are used to detect antibodies binding to specific tissues, often employed in diagnosing conditions like pemphigus and pemphigoid.
- **Flow Cytometry:** Flow cytometry can be used to analyze immune cell populations, helping to identify abnormalities in the immune system.
- **Enzyme-Linked Immunosorbent Assay (ELISA):** ELISA tests are commonly used for quantifying antibody levels in the blood and are employed in many autoimmune disease diagnostics.
- **Western Blot:** Western blotting can be used to confirm the presence of specific antibodies.
- **Immunoprecipitation:** This technique can identify autoantibodies associated with certain autoimmune diseases, such as myositis-specific antibodies.
- **Inflammatory Markers:** Tests like erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) measure inflammation levels and are often elevated in autoimmune diseases.
- **Complete Blood Count (CBC):** Anemia, leukopenia, and thrombocytopenia are common findings in various autoimmune disorders.
- **Immunoglobulin Levels:** Abnormalities in immunoglobulin levels (IgG, IgA, IgM) can indicate immune dysfunction.
- **Specific Organ Function Tests:** Depending on the suspected autoimmune disease, specific organ function tests (e.g., liver, kidney) may be conducted.
- **Biopsy:** In certain cases, a tissue biopsy may be necessary to confirm a diagnosis. This involves removing a small sample of tissue from an affected organ (e.g., skin, kidney) and examining it under a microscope to detect signs of autoimmune-related damage.

The choice of tests depends on the suspected autoimmune disease, clinical presentation, and the physician's judgment. Often, a combination of tests is necessary to establish a diagnosis. Interpretation of these results should be done in the context of clinical symptoms, medical history, and other diagnostic findings to ensure accurate diagnosis and appropriate management of autoimmune diseases (Saschenbrecker et al., 1974).

8.2 Autoantibodies as diagnostic tools

Many autoimmune diseases involve the production of autoantibodies, which are antibodies that target the body's own tissues. Autoantibodies serve several important roles in the diagnosis, prognosis, and management of autoimmune disorders. Here's why autoantibodies are used in diagnosis of autoimmune disorders.

- **Specificity:** Autoantibodies can be highly specific for certain autoimmune diseases. For example, antinuclear antibodies (ANA) are associated with systemic lupus erythematosus (SLE), and anti-cyclic citrullinated peptide (anti-CCP) antibodies are specific to rheumatoid arthritis. The presence of these autoantibodies in a patient's blood can strongly support a diagnosis.
- **Differential Diagnosis:** Autoantibodies can help distinguish between different autoimmune diseases that may present with similar clinical symptoms. For example, the presence of anti-dsDNA antibodies is a characteristic feature of SLE, helping to differentiate it from other rheumatic diseases.
- **Early Diagnosis:** Autoantibodies can be detectable in blood before clinical symptoms fully manifest. This provides an opportunity for early diagnosis and intervention, which can be critical for managing autoimmune diseases effectively.
- **Disease Severity:** The presence and levels of specific autoantibodies can sometimes correlate with disease severity. High titers of certain autoantibodies may indicate a more aggressive form of the disease.
- **Risk of Complications:** In some autoimmune diseases, the presence of particular autoantibodies can indicate an increased risk of specific complications. For instance, in systemic sclerosis (scleroderma), the presence of anti-Scl-70 antibodies is associated with a higher risk of lung involvement.
- **Treatment Efficacy:** Autoantibodies can be used to assess the effectiveness of treatment. A decrease in autoantibody levels may indicate a positive response to therapy, while persistent high levels may suggest treatment resistance.
- **Personalized Medicine:** Knowing the specific autoantibodies present in a patient can guide treatment decisions. Some therapies may be more effective for individuals with specific autoantibodies. Autoantibodies can sometimes predict how an individual will respond to a particular treatment. This allows for a more personalized approach to autoimmune disease management.
- **Research and Drug Development:** Autoantibodies often target specific proteins or pathways involved in the autoimmune response. Understanding these targets can lead to the development of targeted therapies aimed at reducing autoantibody production or their downstream effects. Ongoing research into autoantibodies can lead to the discovery of new biomarkers, helping to improve the diagnosis and management of autoimmune diseases.

8.3 Autoantibody as biomarkers

Biomarkers are measurable indicators that provide insights into disease presence, progression, and treatment response (Florea et al., 2019). Autoantibodies serve as valuable biomarkers in autoimmunity, aiding in the early diagnosis, differentiation of diseases, assessment of disease activity, and prediction of treatment responses (Jing Wu et al., 2017). They are a critical component of the diagnostic and therapeutic arsenal for autoimmune diseases, contributing to more precise and personalized patient care.

In autoimmune diseases, biomarkers are used to.

- **Predict Disease Risk:** Some genetic markers are associated with an increased risk of developing autoimmune diseases.
- **Confirm Diagnosis:** Autoantibodies like rheumatoid factor (RF) and anti-CCP in rheumatoid arthritis or antineutrophil cytoplasmic antibodies (ANCA) in vasculitis help confirm diagnoses.
- **Monitor Disease Activity:** Biomarkers such as ESR, CRP, and certain cytokines can track the level of inflammation and disease activity over time.
- **Predict Treatment Response:** Biomarkers can help predict how an individual may respond to specific treatments, aiding in personalized medicine approaches.
- **Assess Organ Damage:** Biomarkers might reflect tissue or organ damage, such as kidney function markers in lupus nephritis.

Diagnostic Testing with Autoantibody: Autoantibody testing is a crucial diagnostic tool in autoimmune disorders. It involves the detection and measurement of specific autoantibodies, which are antibodies produced by the immune system that mistakenly target the body's own cells, tissues, or proteins. These tests are used to confirm the presence of an autoimmune disease, determine its subtype, assess disease activity, and monitor the patient's response to treatment. Examples

- **Antinuclear Antibodies (ANA):** ANA testing is used to detect antibodies that target the cell nucleus. It is a screening test for various autoimmune diseases, including systemic lupus erythematosus (SLE) and systemic sclerosis (scleroderma).
- **Anti-Double Stranded DNA (anti-dsDNA) Antibodies:** These antibodies are highly specific for SLE and are often used to confirm the diagnosis.
- **Anti-Cyclic Citrullinated Peptide (anti-CCP) Antibodies:** Anti-CCP antibodies are associated with rheumatoid arthritis and are used to aid in its diagnosis.
- **Anti-SSA (Ro) and Anti-SSB (La) Antibodies:** These antibodies are associated with Sjögren's syndrome.
- **Anti-citrullinated protein antibodies (ACPAs):** These are another marker used in the diagnosis of rheumatoid arthritis.
- **Antineutrophil Cytoplasmic Antibodies (ANCA):** ANCA testing is used to diagnose vasculitides such as granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA).

8.4 Imaging techniques for identifying affected organs

Imaging techniques are essential for identifying affected organs in autoimmune diseases. They allow healthcare professionals to visualize structural changes, inflammation, and damage in various organs and tissues. The choice of imaging modality depends on the specific autoimmune disease, the suspected organ involvement, and the clinical presentation. Here are some common imaging techniques used in autoimmunity (Sun et al., 2022).

- **X-Rays:** X-rays are often used to assess joint damage and bone erosions in autoimmune diseases like rheumatoid arthritis. They can reveal changes in bone density and joint space narrowing.
- **Ultrasound (US):** Ultrasound is valuable for evaluating soft tissues and joints. It can detect synovitis (inflammation of the synovial lining) and joint effusions in diseases like rheumatoid arthritis and lupus.
- **Computed Tomography (CT):** CT scans provide detailed cross-sectional images of the body. They are useful for assessing lung involvement in autoimmune diseases like systemic sclerosis and for identifying structural abnormalities in the abdomen and pelvis.
- **Magnetic Resonance Imaging (MRI):** MRI is highly sensitive for detecting soft tissue abnormalities, inflammation, and damage. It is commonly used in autoimmune diseases to assess joint, muscle, and central nervous system involvement. Inflammatory lesions in the brain and spinal cord can be seen in conditions such as multiple sclerosis.
- **Dual-Energy X-ray Absorptiometry (DXA):** DXA scans are used to measure bone density and assess the risk of osteoporosis, which is common in autoimmune diseases, particularly in patients on long-term glucocorticoid therapy.
- **Positron Emission Tomography (PET):** PET scans are used to detect areas of increased metabolic activity, often indicating inflammation. They can be valuable in assessing vasculitis and tracking disease activity in conditions like large vessel vasculitis (e.g., giant cell arteritis) and systemic vasculitis.
- **Single Photon Emission Computed Tomography (SPECT):** SPECT imaging is used for assessing blood flow and tissue viability, which can be useful in diagnosing conditions like lupus nephritis (kidney involvement in systemic lupus erythematosus).
- **Endoscopy:** Various endoscopic procedures, such as colonoscopy, esophagogastroduodenoscopy (EGD), and bronchoscopy, are used to visualize the mucous membranes of the gastrointestinal tract, respiratory tract, and other internal organs to assess inflammation, ulcers, and damage.
- **Doppler Ultrasound:** Doppler ultrasound is used to assess blood flow, and it can be applied to evaluate vascular involvement in autoimmune diseases, such as Raynaud's phenomenon in systemic sclerosis or vasculitis.

- **Fluoroscopy:** This real-time imaging technique is often used in procedures like barium swallow studies to assess swallowing function and identify esophageal involvement in autoimmune diseases like systemic sclerosis.
- **Capsule Endoscopy:** This is a non-invasive method for visualizing the small intestine, and it can be useful in diagnosing conditions like celiac disease.
- **Scintigraphy:** This nuclear medicine technique involves the injection of a radioactive tracer, which is tracked to assess various organ functions or abnormalities.

The choice of imaging modality depends on the clinical context and the specific questions that need to be answered in the evaluation of autoimmune diseases (Procaccini et al., 1999). Multimodal imaging and a multidisciplinary approach involving rheumatologists, radiologists, and other specialists are often necessary to accurately diagnose and monitor these complex conditions.

9. Current treatment strategies

Immunosuppressive drugs such as CNIs and mammalian target of rapamycin (mTOR) inhibitors have significantly boosted graft survival over the last few decades. Monoclonal antibodies and fusion receptor proteins are promising therapeutics for immunosuppression maintenance, either alone or in combination. Monoclonal antibodies (mAbs) are immunoglobulins that are tailored to specifically target an antigen's epitope. Monoclonal antibody therapeutics (MATs) are a fast-growing class of biological medications that are used to treat a wide range of disorders. The increased usage of MATs has a growing impact on clinical laboratory medicine. Biologics have revolutionized the pharmaceutical industry and medical practice providing new hope to patients. Personalized medicine is a health-care delivery strategy that combines preventive, personalized, participative and predictive measures. It is a method for improving treatment by determining a person's disease-causing genetic makeup. A wide range of disorders that can be diagnosed using personalized medicine. A promising future lies ahead for this emerging field.

9.1 Immunosuppressive drugs and their mechanisms

Successful immunosuppression is necessary for organ transplantation. Our thorough understanding of the immunological systems responsible for tissue rejection, along with certain improvements in surgical methods, have led to the majority of contemporary advancements in tissue transplantation. The development of various effective immunosuppressive drugs during the past 20 years has greatly aided the field of transplant therapy. The advancement of tissue transplantation's success rate has depended on the development of efficient immunosuppressive therapies. Immunosuppressive medications have also been used to treat various autoimmune diseases and to protect new-borns from developing Rh hemolytic disease, in addition to organ transplantation (Khan, 2016,

pp. 131–156). Immunosuppressants are categorized based on their mode of action. CsA and tacrolimus are both CNIs. They attach to immunophilins and inhibit the activity of calcineurin. This reduces the synthesis of IL-2 and the multiplication of T cells, both of which are essential for immunological response. Tacrolimus interacts to the immunophilin FKBP12, whereas CsA binds to the immunophilin cyclophilin. Tacrolimus and FKBP12 complex reduces the calcium dependent protein phosphatase activity of the calcineurin-calmodulin complex, reducing both T lymphocyte signal transduction and IL-2 transcription by preventing TNF gene transcription (Flanagan et al., 1991). CNIs cause vasoconstriction in the kidney, which leads to interstitial fibrosis when combined with transforming growth factor overexpression (Burdmann et al., 2003). Rapamycin (Sirolimus) and Everolimus (EVL) are mammalian target of rapamycin (mTOR) inhibitors that have been licensed as antirejection therapies in solid organ transplantation (Fantus et al., 2016). Combining these medications with FKBP12 inhibits mTOR and prevents the translation of mRNA-encoding proteins required for the cell cycle, hence lowering cytokine production and IL-2-mediated T cell proliferation. They appear to have no effect on the initial stages of T-cell activation, in contrast to CNIs (McDermott & Girgis, 2018; Thaunat et al., 2016). Muromonab-CD3 is the first monoclonal antibody that is specifically directed against the CD3 marker on all mature human T cells, was approved for use in solid-organ transplantation (Holt, 2017). Rituximab is a murine/human chimeric monoclonal antibody that targets the CD20 surface marker on B cells directly (Furiasse & Kobashigawa, 2017). Basiliximab, a murine/human chimeric monoclonal antibody, suppresses T cell proliferation by competitively blocking CD25 complex, the alpha subunit of the IL-2 receptor found only on activated and non-resting T cells (Nguyen & Shapiro, 2014). Daclizumab is a humanized monoclonal antibody with high specificity and affinity against the CD25 complex (Nguyen & Shapiro, 2014).

Antithymocyte globulin is a polyclonal antibody that reduces the amount of circulating T lymphocytes by antibody-dependent cell-mediated or complement-dependent cytotoxicity, and their contact with T cell surface antigens may result in apoptosis, which changes T cell activation and homing (Thaunat et al., 2016).

9.2 Targeted biologics and monoclonal antibodies

Biologics have transformed the pharmaceutical industry and medical practice, bringing new hope to patients for whom standard medicines had failed or therapeutic choices were unavailable. Although biologics have become a mainstream and well-defined part of clinical practice, their development has been a long and winding journey. Each stage of development has presented new problems, but it has also catalyzed some of the most prolific and exciting advancements in biotechnology (Rodgers & Chou, 2016). The emergence of biologics for long term maintenance therapy represents a more fundamental shift in the immunosuppressive landscape. Because of the specificities of their targets, the importance of the pathways that they inhibit, the lack of side effects

associated with traditional immunosuppressive agents and the route of administration, the mAbs and fusion receptor proteins in the transplant pipeline have the potential to be transformational in scope. These compounds have extensive half-lives and prolonged physiological effects due to their human/humanized backbone, necessitating intermittent administration. Clinical trials using biologics, on the other hand, are difficult and may have higher failure rates than those with small compounds, as seen by the number of rejected antibodies: anti-CD154 (CD40L) mAbs, efalizumab, anti-CD86/80 mAbs and TGN1412, the super agonist mAb to CD28 (Vincenti & Kirk, 2008). Hu5C8, a humanized mAb to CD154, was the first biologic used for maintenance therapy (Kirk et al., 1999). B cells and the humoral alloimmune response are inhibited when the CD40¯CD154 pathway is blocked. Similarly, blocking the CD40¯CD154 route suppresses T-cell activation, which is dependent on the CD40¯CD154 pathway via CD80/86 over expression. Anti-CD154 treatment in nonhuman primate kidney transplantation was particularly efficient in extending graft life (Vincenti et al., 2010). The first CNI-free and steroid-free clinical trial in kidney transplantation with Hu5C8 delivered intravenously every 2–4 weeks was discontinued due to thromboembolic complications in multiple patients (Kirk et al., 1999). This consequence was most likely caused by the overexpression of CD154 on platelets and its function in clot stabilization (André et al., 2002; Sidiropoulos & Boumpas, 2004). Despite the failure of Hu5C8, the CD40¯CD154 pathway remains a prospective therapeutic target in a variety of diseases, including autoimmune, cancer, and organ transplantation. Several new antibodies are being developed to target CD40, which is not found on platelets and does not cause the same thrombotic or embolic issues as CD154. It remains to be seen whether anti-CD40 mAbs alone are successful in solid organ transplantation. The concurrent use of anti-CD40 and costimulation blocking may be of higher interest (Kirk et al., 1997; Larsen et al., 1996). In experimental transplant investigations, the combination of CD40¯CD154 inhibition and CTLA4Ig induced indefinite graft survival and, in some cases, tolerance (Kirk et al., 1997; Larsen et al., 1996).

The IL-2 receptor (IL-2R) is made up of three non-covalently binding subunits: IL-2R (CD25, 55 kDa), IL2R (CD122, 70/75 kDa), and IL-2R (CD132, 64 kDa). While the β and γ chains are constitutively expressed, the α chain is exclusively expressed on activated T cells, conferring a high affinity for IL-2 and as a result, T-cell clonal proliferation induced by the cytokine. This α chain (CD25) of the IL2-R is targeted by anti-IL-2 receptor monoclonal antibodies (IL-2Ra). Binding of IL2Ra to CD25 causes IL2-R internalization, which inhibits clonal T cell growth dependent on IL-2. Activation via the IL-7 or IL-15 pathways is one proposed escape route. There are two types of IL2-R antagonists i.e., daclizumab, a humanized form that is no longer utilized and basiliximab, a chimeric variant that is now used for induction therapy in solid organ transplantation (Kandus et al., 2010).

Alemtuzumab (Campath-1H) is a humanized monoclonal antibody that targets the pan-lymphocyte CD52 antigen found on lymphoid and myeloid cells. It is a depleting antibody that causes severe and long-lasting lymphopenia via an Fc-mediated mechanism, hence enabling antibody-dependent cell-mediated cytotoxicity of target cells. The majority of B and T lymphocytes, as well as the majority of NK cells, monocytes and macrophages, and a minor fraction of granulocytes, express CD52. Erythrocytes and hematopoietic stem cells do not express it (Waldmann, 2002).

A transmembrane protein expressed on mature B cells is the CD20 receptor. Rituximab is an IgG1k chimeric monoclonal antibody directed against CD20. It has a high affinity for CD20 and is involved in both complement-mediated toxicity and antibody-mediated cytotoxicity by effector immune cells. The primary effect is shown in peripheral blood circulating B lymphocytes, and to a lesser amount in secondary lymphoid organs (Dhesi et al., 2009).

9.3 Emerging therapies and personalized medicines

The phrase "personalized medicine" refers to the classification of patients based on the prediction of disease risk or therapeutic response utilizing diagnostic tools or processes (Miklos et al., 2017). Personalized medicine is a distinct strategy that refers to adapting medical treatment to patients' unique traits. These medications are created using the genetic configuration of the human genome. It has become the key issue for disease diagnosis, prevention and therapy and personalized medicine is founded on pharmacogenomics and genomics (Schilsky, 2010). The improvement of molecular profile technology to gain access to RNA, DNA and protein will enhance personalized therapy for illness management. Personalized medicine is a sort of tailored treatment that can help with a variety of diseases such as lung cancer, brain tumors, prostate cancer, rheumatoid arthritis, autoimmune diseases and so on (Meyerson et al., 2010). The creation of better therapy choices for patients is an essential element of medical research. Because of the individual heterogeneity in the human proteome, personalized medicinal techniques based on molecular markers and cellular context are relevant. To accurately personalize treatment, which includes aspects such as drug selection and dose, reliable and rapid detection of treatment response is required. Traditional ways of obtaining these readouts include blood and urine tests as well as imaging modalities such as ultrasound, CT, MRI and X-rays, among others, which may be limited in terms of testing frequency, especially if treatment response fluctuates on a timeframe of hours or even minutes. Other developing technologies may overcome the limitations of infrequent assessments to increase the accuracy of treatment response assessment, hence boosting the design of personalized therapies (Blicharz et al., 2018). As personalized medicine advances, new areas of development have included the use of nondrug-based platforms, such as digital therapy to treat conditions such as mild cognitive impairment, substance

abuse, mental health and attention deficit hyperactivity disorder, among others (Cho & Lee, 2019; Davis et al., 2018; Kee et al., 2019). Positron emission tomography (PET) and radioactive labeled medicines are two approaches to personalized therapy for cancer management. Regular assessments of blood samples, urine, and so on were used to ascertain metabolite concentrations and pharmacokinetics (Vyas, 2018). PET is a form of imaging tool used as personalized medicine that uses gamma rays to produce three-dimensional (3D) pictures (Van Tinteren et al., 2002). PET has the advantage of targeting the diseased site by utilizing radiolabeled medicines, which will aid in the development of tailored therapies for treatment as a personalized medicine (Van Dongen et al., 2012).

The pathophysiology of treatment for clear cell renal cell cancer (ccRCC) is to target the Von Hipplelindau (VHL) and inactivation of components present in the signaling pathway. VHL is a biomarker for renal cancer, while other markers include carbonic anhydrase and VEGF. Bevacizumab for bevicizumab, axitinib, sorafinib and temsirolimus are recently developed personalized pharmaceuticals (Motzer et al., 2007). Some people have developed resistance to these medications, and sunitinib is the most often used first-line treatment. To address this issue and improve the success of RCC therapy, medicines should be coupled with an antiangiogenic agent. In a study researchers treated patients with pazopanib and discovered a link between a single nucleotide polymorphism (SNP) and progression-free survival and a stronger response when compared to previous treatment (Xu et al., 2014).

Koczan and colleague's primary goal was to uncover biomarkers that will predict the outcomes of therapy in rheumatoid arthritis patients treated with etanercept, a TNF-blocker. They chose 19 RA (rheumatoid arthritis) patients, seven of whom are non-responders and 12 of whom are responders, and changes in pre-existing genes were observed. The Affymetrix microarray produced a result, which was compared to post-treatment data. After 72 h of treatment, gene expression changes and an excellent (DAS) disease activity score of $28 > 1.2$ is obtained. Some patients develop Interferon (IFN), which causes a poor response to treatment. As a result, it is proposed that early prediction of RA response is achievable when TNF-blockers are taken based on their gene expression, and better medicine may be given based on their gene configuration (Koczan et al., 2008).

Lequerre and colleague's investigated the effect of combining methotrexate with infliximab, observing a response after 3 months. They chose 13 individuals and performed gene profiling on peripheral blood mononuclear cells. Seven of the selected patients are nonresponders and six are responders to the treatment. Baseline RNA hybridization and mRNA transcription occur. When transcription levels were compared to response, downregulation was detected in nonresponders. There are 279 genes that differ in expression between responders and non-respondents (Lequerré et al., 2006).

10. Challenges and future directions

More than 8% of the world's population suffers from autoimmune diseases, which is distinguished by a host immune reaction against self-antigens. Although autoimmune diseases can present in a variety of ways, they are a rather prevalent disease group in the general population. Its etiology is complicated, involving both hereditary and environmental factors. It is generally known that autoimmune disease is caused by gene variations and there is mounting evidence that environmental factors play a key role in the development of various disease manifestations. It is possible to better understand the disease's risk profile and identify underlying biological mechanisms influencing disease pathogenesis by identifying combinations of genetic and environmental variables that interact in autoimmune disease. Microbes can have an impact on a variety of physiological functions, including the immune system, metabolism, and behavior. Numerous studies in recent years have emphasized the part played by the microbiome in the etiology of autoimmune disorders. As a result, there is an urgent need for the creation of novel medications or the repositioning of existing ones based on a molecular and clinical understanding of the unique autoimmune diseases in individual patients as well as high-throughput analysis of integrated information. Therapies to treat autoimmune diseases and the involvement of genes, environment and microbiota in autoimmune diseases are the key topics of this chapter.

10.1 Unraveling complex genetic and environmental interactions

Autoimmune diseases develop when a genetically predisposed individual is exposed to an environmental trigger that may be responsible for developing autoimmunity (Doria et al., 2010; Iaccarino et al., 2011; Zen et al., 2011). Autoimmune diseases are a prime example of multigenic diseases. Numerous genetic relationships with autoimmune diseases have been discovered through the use of candidate gene techniques in conjunction with genome-wide association studies (Dai et al., 2010). Infectious agents, ultraviolet light, chemicals or other substances that can modify immune responses, such as environmental pollutants or drugs and behavioral factors, such as smoking and diet are examples of environmental exposures that could be involved in the pathogenesis of autoimmune diseases (Borchers et al., 2010; Ranque & Mouthon, 2010; Selmi, 2011; Selmi & Tsuneyama, 2010; Tobón et al., 2010). The development of autoreactive T cells and autoantibodies, the induction of pro- and anti-inflammatory cytokines and injury to the target end organ are all possible outcomes of additional environmental exposures (Choe et al., 2011; Cutolo et al., 2011). Epigenetics is a novel concept in the field of autoimmunity (Lu et al., 2010). The term "epigenetics" describes changes in gene expression that do not entail modifications to the DNA sequence. It is interesting to note that since epigenetic systems are responsive to outside stimuli, changes in epigenetic regulation can act as a mediator for environmental impacts on immune responses. DNA methylation and

histone modification are the two main methods of epigenetic gene regulation. These two processes cooperate to modify the chromatin structure, which in turn either promotes or inhibits gene transcription. Micro RNAs are one of the recent epigenetic mechanisms to be discovered (Gu et al., 2010; Ooi et al., 2010; Song et al., 2011). The pathophysiology of these disorders is ultimately influenced by the immunological changes that silicon exposure can bring about, such activation of cellular recruitment, cytokine production, Th1-Treg misbalance or reactive oxygen species release (Speck-Hernandez & Montoya-Ortiz, 2012). Immune competence and dietary components, such as vitamins, minerals, and trace elements, have a well-established relationship (Selmi & Tsuneyama, 2010). This implies that certain nutrients may be linked to an increased risk of autoimmune disorders. Recent research has demonstrated how genetic-epigenetic interactions between dietary micronutrients that influence DNA methylation can either worsen or reduce murine lupus (Strickland et al., 2013). Additionally, dietary changes can affect the gut flora, which has been linked to autoimmune diseases (Brown et al., 2012). A high-sodium diet has recently been found to encourage the growth of Th17 helper T cells, which act as mediators of autoimmune inflammation (Chuan Wu et al., 2013). The induction of murine and human Th17 cells, which are responsible for autoimmune diseases, was dramatically enhanced by elevated NaCl concentrations at physiological levels (Kleine-wietfeld et al., 2013).

The field of epigenetics focuses on the chemical alteration of DNA, such as DNA methylation, which has the potential to change gene transcription and subsequently cell function. There is strong evidence that environmental exposures have an effect on epigenetic markers since they are flexible and may change over the course of a person's life (Foley et al., 2009). Smoking, for instance, has been demonstrated to modify DNA methylation at several genomic loci (Breitling et al., 2011; Wan et al., 2012) and there is evidence that numerous other pollutants and chemicals can also alter the epigenome (Feil & Fraga, 2012). Epigenetics thus offers a biological basis for the interaction of environment and genes in autoimmune illnesses and other diseases (Javierre et al., 2011). Epigenetics also offers a conduit via which the environment can influence genes. The third hypervariable region of the HLA DR1 chain, encoded by the DRB1 gene, is where the rheumatoid arthritis "shared epitope" (SE) specifies a group of HLA types that have a common amino acid sequence (Gregersen et al., 1987). As a result of the strong gene-environment interactions between smoking and the presence of the strongest genetic risk factors for RA, HLA-DRB1 shared epitope (HLA SE) and PTPN22, smoking significantly raises the risk of developing RA in people who carry the susceptibility genes (Costenbader et al., 2008; Karlson et al., 2010).

10.2 Developing more specific and safer therapies

Type 1 diabetes (T1D), rheumatoid arthritis (RA), multiple sclerosis (MS), and over 100 other autoimmune diseases (AID) are caused by the immune system of an individual

attacking certain body tissues. The organization of such an attack is carried out by autoantigen-specific T cells, which are typically confined to certain major histocompatibility complex (MHC) molecules and which trigger pathogenic effector T (Teff) cell and humoral responses (Gutierrez-Arcelus et al., 2016). The lack of access to transformative therapies is a significant contributor to the chronic nature of these diseases and the poor quality of life experienced by those who suffer from them. Azathioprine, CNIs, corticosteroids, cyclophosphamide, leflunomide, methotrexate, mycophenolate and other broad cytotoxic or immune suppressive medications are only a few examples of the broad chemicals still used in traditional AID therapies (Cooper & Stroehla, 2003). The Janus kinase (JAK) inhibitors are a new class of low molecular weight chemicals that prevent cytokine receptors from transmitting intracellular signals. Although the specificity of the various JAK family members determines the cytokine selectivity of JAK inhibitors, all of them impede the signaling of a sizable spectrum of cytokines. Several disorders can be treated with JAK inhibitors (Nash & Clegg, 2005). However, as long-term therapy, they may put the patient at risk for malignancies and potentially fatal opportunistic infections (Jamilloux et al., 2019; Winthrop, 2006, 2017).

Therefore, there is a very significant medical need for AID treatments that are efficient, secure, and focused. The development and widespread clinical application of synthetic or biologic drugs that block various immune system pathways and elements, such as cytokines, cell adhesion molecules and costimulatory molecules or eradicate entire immune cell populations have significantly altered the treatment of autoimmune diseases over the past 20 years (Fugger et al., 2020).

Numerous autoimmune disease treatments are being investigated, and they all aim to improve the immune system's anti-inflammatory or tolerogenic function. These treatments are designed to manage autoimmunity and restore immunological tolerance. Emerging as potential therapies for the treatment of autoimmune disease are cell-based medicines. Ex vivo-engineered Tregs that express a receptor, such as a TCR (Bluestone et al., 2015), that is specific for the auto-antigen aggravating the autoimmune disease or a chimeric antigen receptor (CAR) (Dawson & Levings, 2017; Harris & Kranz, 2016) or expanded TR1 cells expressing IL-10 (Desreumaux et al., 2012) are other methods. Other Tregs express a natural repertoire of polyclonal TCRs as well. Additionally, dendritic cells (DCs) provide a cell-based therapeutic approach to improve tolerance and stop autoimmune disease. Immune tolerance may be recovered due to the tolerogenic phenotype that tregs can induce in DCs. Ex vivo-generated tolerogenic DC administration is being investigated since tolerogenic DCs can reduce autoimmune (Giannoukakis et al., 2011). Other methods have expanded antigen-specific Tregs using mature DCs (Yamazaki et al., 2006). To treat autoimmune disease, a wide range of treatment strategies strengthening the immune system's anti-inflammatory component are being investigated. This presents a chance to enhance existing treatment plans, leading to enhancements in patient outcomes. Molecules that support the in vivo induction and

growth of Tregs have been the focus of recent drug-based approaches for reducing autoimmunity. Rapamycin, a medication that inhibits mTOR, as well as biologicals such as the injection of IL-10, low-dose IL-2, TNF receptor 2 (TNFR2) agonists or FMS-like tyrosine kinase 3 ligand (Flt3L) have all been studied (Abbas et al., 2018; M. Battaglia et al., 2005; Manuela Battaglia et al., 2006; Biswas et al., 2015; Chen et al., 2007; Zeiser et al., 2008).

10.3 Role of microbiota in autoimmune disorders

Persons who have autoimmune illnesses experience an imbalance between their immune system's tolerogenic and immunogenic functions. Autoreactive B and T cells that evade central tolerance and respond to self-antigens attacking healthy bodily tissues frequently play a role in pathogenesis (Brzezicka & Paulson, 2023). Multiple interactions may be predisposed to cause autoimmune disorders. In actuality, an environmental trigger causes an autoimmune illness to manifest. As was already established, heredity plays a significant role in the development of autoimmune illness and accounts for roughly half of the risk of developing the condition; the remaining half is brought on by environmental factors. Microbial elements, particularly those that lead to a persistent infection, food, metal, toxins, radiation, and sex hormones like estrogen are some of the most hazardous causes. Additionally, immune system alterations might be brought on by nutritional deficits (Carson, 1992; Selmi & Tsuneyama, 2010). For instance, the innate immune system's NLRP6 and nucleotide-binding and oligomerization domain-containing protein 2 (NBOD2) activities, which are both crucial for bacterial recognition, allow the microbiota to play a significant role (Levy et al., 2015; Petnicki-Ocwieja et al., 2009). Dysbiosis or immune system dysfunction can disrupt the maintenance of homeostasis between the microbiota and the immune system, which can result in an uncontrolled inflammatory condition or breakdown of tolerance and the onset or promotion of autoimmunity (Shamriz et al., 2016).

If the mechanisms of tolerance fail, the microbes can cause the immune response to be directed against the host in various different ways (Agmon-Levin et al., 2009; Getts et al., 2013; Guilherme et al., 2006; Vanderlugt & Miller, 1996; Vojdani, 2014). Rheumatoid arthritis, systemic lupus erythematosus, and antiphospholipid syndrome are just a few of the autoimmune diseases that have been associated with autoantibodies against the ubiquitous commensal yeast Saccharomyce cerevisiae's cell wall mannan (phosphopeptidomannan), or mannan. Due to the fact that S. cerevisiae is also a vaccine adjuvant, researchers have speculated about a potential risk of aberrant immune activation that could be related to an autoimmune/inflammatory syndrome induced by adjuvants (ASIA) (Rinaldi et al., 2013; Shoenfeld & Agmon-Levin, 2011). Inflammatory bowel disease such as Crohn's disease (CD) and ulcerative colitis (UC), provide as an illustration of how changes to the gut microbiome can lead to disease. Notably, multiple

investigations have demonstrated that both CD and UC are linked to decreased commensal microbiota complexity and recurrent transitions to a dysbiotic condition. Both CD and UC are characterized by the expansion of the phylum proteobacteria, particularly the Enterobacteriaceae family and Fusobacteriaceae (Carding et al., 2015; Frank et al., 2007; Gevers et al., 2014), in a manner similar to what is seen during acute mucosal infections. Additionally, Crohn's disease patients have considerably higher rates of adherent-invasive E. coli, Yersinia, and Clostridium difficile than healthy people (Chassaing et al., 2011; Lamps et al., 2003; Navaneethan et al., 2010). The percentage of several Bacteroides, including Bacteroides stercoris, Bacteroides coprocola and Bacteroides coprophilus, Faecalibacterium and short-chain fatty acid (SCAF) producing bacteria decreases in Multiple sclerosis (MS) patients, while Methanobrevibacter, Enterobacteriaceae and Akkermansia increases (Miyake et al., 2015). Numerous researchers have suggested that dysbiosis may also play a role in the etiology of type 1 diabetes mellitus (T1DM) (Qi et al., 2016).

High concentrations of antibodies against these microorganisms have been observed in the blood and synovial fluids of patients with rheumatoid arthritis (RA), and oral bacteria including Prevotella intermedia and Tannerella forsythia have been found in the oral flora (Caminer et al., 2017). In contrast, IgG antibodies against P. intermedia and C. ochracea were linked to a decreased incidence of rheumatoid factor, according to previous researchers (Goh et al., 2016; Lange et al., 2016; Roszyk & Puszczewicz, 2017).

In fact, a lower Firmicutes/Bacteroidetes ratio and the abundance of several genera were found in patients with Systemic Lupus Erythematosus (SLE). Rhodococcus, Eggerthella, Klebsiella, Prevotella, Eubacterium, and Flavonifractor were significantly enriched, while Dialister and Pseudobutyrivibrio were decreased (He et al., 2016; Hevia et al., 2014). Notably, the scientists hypothesized that patients with Antiphospholipid syndrome may harbor the anaerobic gram-positive bacterium Roseburia intestinalis in their guts (Ruff et al., 2015).

Sjogren's syndrome (SS) and EBV/Coxackie virus infections have been linked closely in a number of studies (McClain et al., 2005; Stathopoulou et al., 2005). In fact, Ro60 reactive T-cells may be activated by peptides produced from commensal oral, intestinal, and cutaneous bacteria. Prevotelladisiens, Capnocytophagasputigena, and Capnocytophagaochracea are found in the oral flora, Bacterioidesfinegoldii, Bacteroides intestinalis, Bacteroides fragilis, and Alistipesfinegoldii are found in the gut flora, and Corynebacterium amycolatum and Acinetobacter johnsonii are found on the skin (Szymula et al., 2014). As a result, oral dysbiosis has been linked to an increase in Firmicutes, particularly Streptococcus and Veillonella, and a decrease in Synergistetes and Spirochetes in SS patients (Siddiqui et al., 2016). It was also found that the amount of the genus Faecalibacterium, which includes Faecalibacteriumprausnitzii, one of the major butyrate makers in the colon, was reduced by about 50% in fecal samples from SS patients (De Paiva et al., 2016).

It is well documented that Systemic sclerosis (SSc) patients have higher levels of Fusobacterium and Proteobacteria and lower levels of commensal bacteria such Faecalibacterium and Clostridium when compared to healthy controls. However, Bifidobacterium and Lactobacillus, which are generally lowered during an inflammatory state, were also raised in SSc patients (Volkmann et al., 2016).

11. Patient management and quality of life

2020 has been one of the brutal years for global health. Health services are working to fight Covid-19 and provide life-saving care. The pandemic has far-reaching consequences for the world. Some examples are public health crisis, economic disruption, travel restrictions, education disruption, supply chain disruption, vaccine development, impact on mental health, etc. It even threatens to undo the hard-won global health gains of the past 2 decades in the fight against infectious diseases. Even after facing these challenges, WHO is working to prepare for this kind of health emergency.

The World Health Organization defines health as "*a state of complete physical, mental and social well-being and not just the absence of disease or infirmity*". As such, health care can be understood as the improvement of health through the prevention, diagnosis, prompt treatment, improvement or cure of disease, injury or even other physical and mental impairment of health in humans. Healthcare is provided by medical professionals and various fields of allied health.

Patient care and quality of life are two essential aspects of healthcare. Patient care includes a variety of activities aimed at providing optimal care for each individual. It integrates diagnosis and assessment, treatment planning, monitoring the health progress, educating patients about their condition for better health management and care coordination. As in many complex cases, multiple health care providers may be involved. Thus, effective communication is ensured so that the patient receives comprehensive care.

On the other hand, quality of life refers to the overall well-being and satisfaction of the patient. It is not limited to curing disease but also refers to the physical, emotional, psychological and social aspects of a person's life.

Quality of life can be improved through a variety of ways and means that can be related to pain control by controlling it satisfactorily, as uncontrolled pain reduces quality of life. Psychosocial support can be provided by addressing mental and emotional health through counseling and support groups or therapy, etc. To improve quality of life, rehabilitation also plays an important role as it helps a person regain functionality and independence. In addition, encouraging patients to adopt a healthy diet and be physically active can also improve their overall health. Therefore, the ultimate goal of patient care is not only to treat the disease, but also to help them improve their quality of life, thereby helping them to have a fulfilling life despite health problems.

11.1 Psychological impact of chronic autoimmune disorders

In a diverse arena of psychology, one of the specialties is the health psychology within the mental health field that considers social, biological, behavioral and psychological factors that impact the human health and illness. Thus, professionals working in this field aims to improve healthcare systems, illness prevention thereby promoting habits leading to better health outcomes.

There should not be any doubt in believing the fact that illness or diseases that directly affect brain can have a strong psychological impact on humans (Koenig & Cohen, 2002, pp. 174–196). This has been seen especially in the patients of chronic autoimmune disorders. Since, these disorders are long lasting, patients tend to get stressed due to such long-term health issues which with no doubt disturbs their work life balance, personal lives and what not. Even studies have shown that the people suffering from these chronic autoimmune conditions like lupus, ankylosing spondylitis and colitis are directly associated with an increased risk of mental health problems such as depression and bipolar disorder. According to various epidemiologic studies, a positive link has been established between autoimmune diseases and psychosis, a severe mental disorder wherein the person loses contact with external reality due to impaired thoughts and emotions (Jeppesen & Benros, 2019).

Thus, the symptoms such as irritability, trouble concentrating and making decisions, loss or gain of weight, depression leading to suicidal tendencies, etc. can be observed. This can directly affect one's efficiency of working and hence, the person may even face difficulties in adjusting in the surrounding as well. Therefore, it is important to be aware of the possible mental health symptoms.

11.2 Multidisciplinary approach to patient care

A group of experts from two or more disciplines who work on the same plan independently or concurrently are referred to as a multidisciplinary team. In the context of healthcare, "collaboration" refers to a problem-solving process, shared decision-making authority, and the capacity to implement a treatment plan while pursuing a shared objective.

Multidisciplinary approach to patient care has proven to be more effective as compared to traditionally followed individual plan of patient care where just the doctor and patient are involved. It is an integrated team approach to healthcare, where the improvement and implementation of patient-centered treatment plans is a shared responsibility among skilled professionals (Castro & Wang, 2023). The team in multidisciplinary approach incorporates doctors, nurses, dieticians, medical and paramedical staff along with the patient and their family and caretakers (Epstein, 2014). The major goal of this approach is to help patients achieve the best level of functioning and awareness of their care, by understanding and addressing all aspects of their illness and needs.

Thus, adopting multidisciplinary approach definitely helps achieve various goals such as providing better care coordination, especially across various care locations or specialties thereby improving patient satisfaction. It also helps give better treatment and quality care and hence, better patient outcomes can be achieved through this approach (Leeftink et al., 2020).

A multidisciplinary approach can also simplify the treatment pathways and help achieve less duplication of services. This will ultimately decrease in hospital admissions.

11.3 Fundamentals that make multidisciplinary care an effective approach in healthcare sector

- It is a team-based approach where healthcare experts, the general practitioner, and related healthcare professionals deal with not only the treatment plans and implementation of care but also the psychosocial aspects of care.
- It ensures regular communication with team members.
- It provides access to a complete range of therapeutic options, irrespective of geographical remoteness, rural or urban healthcare service.
- The patients are included in their care discussions and management and it is ensured that they receive timely and appropriate information from healthcare professionals.

In short, the multidisciplinary care approach results in greater patient satisfaction with treatment, improved financial performance, reduced median length of hospital stay, and a significant reduction in unplanned readmissions (Sierchio, 2003).

11.4 Lifestyle modifications and support systems

The people's choices in relation to areas like alcohol consumption, diet habits, and smoking have the potential to critically affect their health. A poor diet, smoking is the modifiable behaviors and also is the significant contributors of poor outcomes.

The patients can be encouraged by their family physicians by using brief, evidence-based techniques in order to change their unhealthy behaviors. The health improvement can thus be tracked by the patients themselves and by developing health goals and eliminating the barriers a good outcome in terms of health can be achieved.

The role of healthcare professionals in lifestyle modification is basically to promote and disseminate information on nutrition, physical activity and maintenance of a healthy weight. Apart from this, their role becomes important in encouraging patients to set achievable goals and to identify the barriers and ways to overcome the challenges (Treciokiene et al., 2021).

Lifestyle modifications and the support systems are two important aspects in order to achieve a healthy lifestyle. Lifestyle modifications relates to the changes in habits or behaviors that can improve health and prevent diseases. Whereas, support systems in healthcare includes people and programs that can assist and help individuals in order to achieve their set lifestyle goals and cope up with challenges.

To achieve a healthy lifestyle, there are several habits and behavior that can be adopted such as eating a healthy diet, increasing physical activity, quitting smoking and consumption of other unhealthy and harmful drugs, managing stress by various techniques like meditation, sports, etc. and to achieve this, advice and support of professionals can be taken in the form of support systems which includes healthcare professionals, family members, friends, self − help groups and other communities (Thompson, 2019).

12. Prevention and public health implications

Prevention strategies for autoimmune disorders are challenging because these conditions often result from complex interactions between genetic, environmental, and immunological factors. While it may not be possible to prevent autoimmune disorders entirely, there are several approaches and strategies that can reduce the risk of developing these conditions or help manage their symptoms.

12.1 Early intervention strategies

In the interest of public health, the age-old fact "prevention is better than cure" is of great significance. Early intervention strategies represent a proactive approach in safeguarding and enhancing the welfare of individuals and society. It aims to soothe health risks, less healthcare costs, and overall well-being of mankind.

Autoimmune diseases including rheumatoid arthritis, lupus, multiple sclerosis, diabetes type 1, etc., occur when the body's immune system mistakenly attacks its own tissues. These chronic conditions are devastating, impact millions of individuals and pose substantial economic burdens on healthcare systems. Therefore, focusing on early intervention strategies not only improve patient outcomes but also address the wider public health implications. For an example, it is now possible to profile genetic risk at birthin type 1 diabetes mellitus (T1D) to identify suitable intervention tactics.

Recently, optimal time for treating high-risk Smoldering Multiple Myeloma (SMM) has been inferred from the analysis and investigations, wherein, differences in progression, mortality rate and response rate has been illustrated (E. Bridget Kim et al., 2020).

Here are some strategies for early intervention.

- Improvements in diagnosis and a screening methods.
- Development of new and selective therapies.
- Implementing the education for personalized medicine which can tailor the treatment to each patient's individual characteristics.

Thus, it can be said that early intervention strategies are the bedrock of a proactive approach to public health. These are important for the better health outcomes and improved quality of life with such chronic conditions. By focusing on prevention, we can reduce the chances of occurring of disease, enhance the quality of life, and pave the way for a healthier and more prosperous future. Public health organizations,

policymakers, and individuals must continue with these strategies and procedures, recognizing their major role in promoting well-being and safeguarding our overall health.

12.2 Public Awareness Campaigns

Public Awareness Campaigns play a crucial role in preventing autoimmune diseases. To combat the rising prevalence of autoimmune diseases, public awareness campaigns play a keen role in empowering society (Bugshan et al., 2022).

As per Research studies, public awareness campaigns can significantly impact the prevention of such severe diseases. In context with the origin of such complex diseases, like adult-onset neurodegenerative diseases, cancers and metabolic disorders, the condition becomes much more challenging, as the causes of most of these diseases still remain unidentified. Thus, understanding the onset of such chronic diseases allow early identification of patients with threatening autoimmunity, reveal new therapeutic targets, and allow interventions to prevent autoimmunity.

In terms of early Rheumatoid arthritis, understanding its natural history and characteristics have brought this field to a threshold of preventive strategies accepting the risks and costs involved. Spreading awareness about such severe diseases is the foremost objective of these awareness campaigns. Many individuals are unfamiliar with these chronic conditions, which leads to delayed diagnosis and treatment. Thus, providing early symptoms and prompt medical advice plays a significant role in preventing such conditions (Bugshan et al., 2022).

Early diagnosis is pivotal in managing autoimmune diseases effectively. Public awareness campaigns highlight the importance of regular health check-ups and screenings. By spreading awareness, empowering patients, detecting diseases early, researching, these campaigns aim to create a more acquainted and compassionate society.

12.3 Potential for vaccines against specific autoimmune triggers

Vaccination is a potential strategy for preventing and treating autoimmune diseases by targeting specific autoimmune triggers. But what are these autoimmune triggers? These triggers are the factors activating the immune system to attack the body's own cells and tissues. These triggers can be viruses, bacteria, toxins, drugs, stress, hormones, and dietary components. For instance, in rheumatoid arthritis, the joints whereas in multiple sclerosis, the CNS is attacked causing chronic inflammation (Olivieri et al., 2021).

As per the findings of eClinicalMedicine, suite of journal covering clinical research from all medical specialties, Covid 19 is linked with acquiring various autoimmune diseases whereas its vaccination significantly attenuated the risks of these autoimmune diseases.

The prevention and public health implications of using vaccines for autoimmune diseases are manifold. By being more specific, cheaper and secure, it can offer several

advantages over conventional treatments. Apart from this, vaccines also offer positive spillover effects on other aspects of health, such as preventing infections and cancers, enhancing immunity, and promoting healthy behaviors. Researchers are looking out at the possibilities of vaccines to target the specific triggers of autoimmune diseases owing to their potential of defense against specific pathogens. Preventive and therapeutic vaccines can be used for this purpose (Vadalà et al., 2017).

Preventive vaccines prevent such chronic conditions from developing in individuals who are susceptible, by inducing tolerance to self-antigens or eliminating infectious triggers. The therapeutic vaccines treat existing autoimmune diseases by modulating or reversing the immune response which causes tissue damage. Since the research is in its early phases, creating vaccines against autoimmune triggers could pose various challenges.

- **Autoimmune Complexity:** Autoimmune diseases are greatly complex. Thus, the triggers can fluctuate from individual to individual making the development of vaccines covering a diversified range of autoimmune triggers a formidable task.
- **Safety Issues:** Vaccination against autoimmune diseases may induce safety concerns. The immune system must be stimulated carefully to not actuate new autoimmune responses or other unintentional consequences.

It is a budding strategy for preventing and treating autoimmune diseases by targeting specific autoimmune triggers. However, many challenges and limitations can arise in developing and testing vaccines for such severe conditions including identification of relevant antigens and triggers, designing the optimal vaccine formula and methods of delivery, ensuring safety and efficacy in diverse communities, overcoming ethical and regulatory obstacles, and confronting public perception and acceptance.

Certainly, the implementation of vaccines against specific autoimmune triggers is an optimistic approach in medical research. Though it is a work in progress, it provides hope to millions affected by autoimmune diseases worldwide. However, it is important to advance in this field of study with absolute caution with detailed research and experiments. Autoimmune diseases have been a medical mystery for ages which is finding its way to be resolved with continuous research and scientific developments.

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CHAPTER 4

Systemic autoimmune disorders

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1. Introduction

Autoimmunity is an abnormal condition wherein immune system fails to discriminate between self and non-self elements. It is a breach of tolerance where body reacts against its own tissue constituents. This kind of reaction results in an adverse state characterized by a specific immune activation against the body's self tissues (auto antigens). Immune reaction toward self antigens is manifested clinically by the incidence of autoreactive T cells and autoantibodies. There are more than 80 distinct autoimmune diseases which affect 5%–7% of the population. The increasing prevalence of autoimmune diseases represents a threat to public health across the world in developed as well as developing countries (Lerner et al., 2015; Patterson et al., 2009). Autoreactivity and genetic predisposition to autoimmunity are the two critical facts for understanding their increasing prevalence (Cho & Gregersen, 2011; Gutierrez-Arcelus et al., 2016), probably because the genetic factors have ability to defend against infectious disorders (Liao et al., 1995; Liu et al., 2009). Moreover, few studies regarding the genetic background of autoreactivity explain that the genetic traits governing autoimmunity are distinctive from the traits controlling particular tissue vulnerability (Liao et al., 1995; Liu et al., 2009) or tissue damage severity (Martini et al., 2014). Hence individuals might possibly share pathway leading to autoimmunity, yet having diverse autoimmune disorders (Cho & Gregersen, 2011; Cotsapas et al., 2011). Individuals with a single autoimmune disease are more susceptible for second autoimmune disease (Cooper et al., 2009; Jacobson et al., 1997; Marrie et al., 2015).

In autoimmune conditions tissue destruction occur by antibody or T-cell reactivity against the self components. The immune reaction might be prompted by infection and then persevere without the presence of any evident bacterial or viral antigen (Davidson & Diamond, 2001; Rose & Bona, 1993). Although various diseases described as autoimmune exhibit reactivity toward self, evident facts about the self-reactivity could still be missing. Animal models regarding autoimmune disorders have contributed enormously to improve our knowledge of both disease inception and its pathophysiology (Bar-Or et al., 2011; Billiau & Matthys, 2011; Howell, 2002; King, 2012; Lam-Tse et al., 2002; Mandik-Nayak & Allen, 2005; Peutz-Kootstra et al., 2001; Wooley, 2004).

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Various autoimmune disorders develop spontaneously in animals while some are triggered by inoculation with self-antigen or adjuvants. Although animal models are extremely significant in explaining autoimmunity, but how directly they reveal human disease is still unknown (Bodaghi & Rao, 2008; Kollias et al., 2011). Some are more identical in the effector patterns of tissue destruction than in autoreactivity induction mechanisms. In fact, tissue damage mediated by autoantibody is perhaps most parallel in animal models and human disorders (Monach et al., 2004).

Autoimmune diseases are multifaceted diseases resulting from a union of environmental, genetic and stochastic factors—that collectively work to instigate the hallmarks of disorder that is dysregulated immune response against self antigenic elements and consequent organ injury. It is apparent from studies of animal models and epidemiologic studies that genetic component is essentially associated with all autoimmune diseases. Very few autoimmune disorders seem to be monogenic disorders (Melki & Crow, 2015). However, many susceptibility loci have been shown to contribute to the phenotype for many autoimmune disorders. Studies using mouse models have also demonstrated the presence of locus that represses the autoimmune disorder phenotype (Wakeland et al., 2001). Hence the risk to develop autoimmune disorder depends on resistance locus as well as susceptibility. With the recent introduction of genome-wide association studies (GWAS) novel genes have been recognized in autoimmunity. In addition, GWAS has evaluated huge number of single nucleotide polymorphisms (SNPs) as genetic biomarkers in well-defined patients and healthy controls. A number of genetic variants have definitively been linked to disease susceptibility in multiple autoimmune diseases (Deng & Tsao, 2010; Flesher et al., 2010; Harley et al., 2008). A lot of these variants are present in non coding areas of a gene and regulate basal expression [eQTL (expression quantitative trait loci)] or expression subsequent to stimulation (response eQTLs) (Gutierrez-Arcelus et al., 2016; Wang et al., 2015).

Autoimmune diseases are regarded as polygenic diseases, including both major histo compatibility complex (MHC) and non MHC genes (Jones et al., 2006; Wandstrat & Wakeland, 2001). The exact association of MHC polymorphisms with autoimmune disease is still unknown but possibly may be because of T-cell identification of particular immunogenic peptide that binds within the peptide binding cleft of various MHC molecules, cross-reactivity of self peptides with the peptides derived from pathogen, or variation in the T-cell repertoire leading to the reduction of Tregs (Cho & Feldman, 2015; Raychaudhuri et al., 2012; Sollid, 2017). Except MHC, other genomic loci for autoimmune diseases recognized by GWAS include a collection of around 300 fairly common alleles, all of which endows only a mild risk, having odds ratios of 1.5—2 (Gutierrez-Arcelus et al., 2016; Wang et al., 2015). Few among these polymorphisms cross chief ethnic groups. It is evident from mouse models that genomic susceptibility could be an effect of combination of genes in each genetic locus rather than one gene in each locus. For instance, chromosome one region concerned in systemic lupus

erythematosus has various sub loci contributing to several disease aspects (L. Morel et al., 2001; Laurence Morel, 2010).

Recently, association of non MHC genes with autoimmunity has well been established (Gregersen & Olsson, 2009; Pearce & Merriman, 2006; Wandstrat & Wakeland, 2001). These include genes involved in apoptosis, antigen clearance, cytokine production and cell signaling as well as in the cytokine receptor expression and co stimulatory molecules (Gregersen & Olsson, 2009; Murphy et al., 2008; Pearce & Merriman, 2006; Wandstrat & Wakeland, 2001). Complement components for example are needed for precise removal of immune components, and an elevated rate of C4 homozygous deficiency is described in SLE patients having deposits of immune complex in injured tissues like kidneys (Vratsanos et al., 2001).

The majority of risk genes recognized by GWAS are ordinary variants having negligible effects which are unaffected by standard immune processes; in the majority of subjects, the discrepancy is not in the coding area of the gene but gene expression regulation (Rieck et al., 2007; Zhang et al., 2011). In longitudinal cohorts, gene combinations that indicate the likelihood of developing a disease are beginning to be discovered (Achenbach et al., 2013; Langefeld et al., 2017; Laufer et al., 2017; Lempainen et al., 2015). Monozygotic twin concordance for the majority of disorders is still below 50%, despite breakthroughs in our understanding of the genetics of autoimmunity, suggesting that environment and/or random aspect may also play a functional role.

2. Types of autoimmune diseases

Autoimmune diseases, based on the autoantigenic targets are categorized into systemic autoimmune diseases and organ specific autoimmune diseases. Systemic autoimmune disorders include a broad spectrum of related disorders manifested by immune dysregulation which activate immune reactions against autoantigens and lead to inflammation and multiple consequent tissue destruction.

2.1 Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a systemic immune system disorder causing enormous mortality and morbidity around the world, mainly in the females of reproductive age. It is normally connected with antinuclear antibodies (ANA), explicitly anti double-stranded DNA antibodies (anti dsDNA), forming immune complex that can prompt multiple organ destruction through varied cell types in genetically predisposed individuals. SLE is a typical polygenic disorder; with different genomic variants adding to disease risk. Complement protein deficiencies such as C4 and C1q in classical complement pathway have been associated with SLE. However these aberrations are quite rare and have incomplete penetrance, demonstrating that hereditary as well as environmental component is required. Over 100 autoantibodies (Sherer et al., 2004) were documented

in SLE individuals including ANA, as well as antibodies focused on platelets, endothelial cells, and antigens in the brain. Autoantibody development predates disease onset (Arbuckle et al., 2003). Practically each SLE patient is ANA positive, which might also incorporate particular antibodies connected with organ inclusion. Anti-Sm and anti dsDNA are the most inclusive for SLE; however anti dsDNA antibodies are the most broadly examined autoantibodies in SLE and are additionally special than ANA. Free DNA along with dsDNA antibodies form antibody-antigen complex buildings, which get accumulated in the regions like kidney and skin to trigger immune response and causing organ injury by activated complement and antibody dependent cellular cytotoxicity. Immune complexes containing DNA can likewise trigger immune response via surface and endosomal toll like receptors. The adaptive immune system has apparently been concerned in the SLE etiology given the chief role of auto reactive T and B cells (Moulton et al., 2017), though innate immune system dysregulation is also crucial. Imperfections in anergy, central and peripheral tolerance are known to be implicated in SLE (Malkiel et al., 2016; Yurasov et al., 2005). Intense malar rash which may be light sensitive is a typical feature of SLE. Different types of SLE-related rash incorporate bullous lupus, a maculopapular lupus and epidermal necrolysis lupus rash. Chronic lupus forms include chilblain lupus, lupus panniculitis and discoid rash. The diagnosis of SLE might be done on the basis of three kinds of muco-cutaneous disorder and a positive ANA; hence a cautious evaluation of mucus and skin should be carried out. Jaccoud's arthropathy happens in 5%−10% of SLE patients. Usually impacted locales are the hip and tibial level. Pericardial effusion and pericarditis are the most frequent cardiovascular appearances of SLE. Endocardial and myocardial inflammation, like Libman-Sacks endocarditis, could likewise occur. Infective endocarditis and ischemic coronary illness are general comorbidities in patients who are on long term and high dosage corticosteroids. Individuals with SLE are susceptible for extended cardiovascular disorders and having high rate of venous and arterial thromboembolic episodes in contrast with the healthy people (Mok et al., 2005).

Secondary Raynaud's phenomena occur in 20% of SLE individuals. Neurological signs of SLE could vary from seizures including cranial nerve paralyzes and peripheral neuropathies to psychosis and acute states of confusion (Kozora et al., 2004).

2.2 Sjogren's syndrome

Sjogren's syndrome (SS) is considered as one of the most frequent autoimmune disorder. It may additionally be present as either a primary syndrome or as a secondary syndrome in affiliation with different autoimmune disorders, along with systemic lupus erythematosus (SLE), rheumatoid arthritis, systemic sclerosis and primary biliary cirrhosis (Brito-Zeron et al., 2016; Delaleu et al., 2005). Like with other autoimmune disorders, there is an amazing deal of scientific inconsistency such that a few patients might also have dry

eyes and/or dry mouth, whilst some may additionally have systemic complications such as kidney diseases, lung diseases and lymphoma.

The syndrome is called after Dr. Henrik Sjogren, an ophthalmologist from Sweden, who in 1930 noticed an affected person with less discharge from the lacrimal and salivary glands. While SS once regarded as an extraordinary disease, it's now regarded as the second most frequent autoimmune disorder, after rheumatoid arthritis. Its occurrence is anticipated at 1% (0.1%–4.8%) with an incidence of seven per 100,000 in the United States (Helmick et al., 2008; Thomas et al., 1998). Though SS is known to be a disorder chiefly of females, with a female-to-male ratio of 9:1, the frequency of SS is probably more in adult males than is presently anticipated, due to the fact males generally tend to produce an unusual sample of autoantibodies than women and often are neglected with the modern diagnostic procedures (Beckman et al., 2017).

The clinical expressions that outline the syndrome are dry mouth and dry eyes. It is predicted that the ordinary affected person has had syndrome for 3 years before they are identified (Akpek et al., 2015). Manifestation of the eyes is one of the defining characteristics of SS. Patients experience dryness, gravel like sensation in eyes, and frequently related pain of eyes. Such complications often lead to living alternations (Akpek et al., 2015). SS patients will have difficulties with each lipid and aqueous secretion as well as meibomian gland disorder. Eye symptoms can encompass corneal perforation and ulceration, conjunctivitis episcleritis and scleritis, optic neuritis, uveitis and orbital inflammation each one may be infectious and/or autoimmune (Akpek et al., 2015). Salivary glands involvement is the subsequent distinct complication of SS. SS individuals feels dryness and burning sensation of their mouth; loss of smell and taste senses; eating problems; weight loss and speaking problems. Oral cavity complications involve dry as well as cracked lips, dental caries, gingivitis, oral ulcers, tongue, depapillation and fungal infections (Napenas & Rouleau, 2014). Apart from mouth, however, other problems are also visible. Dysphagia in the esophagus, can be observed due to less saliva. Gastroesophageal reflux along with dysmotility and dysphagia may additionally occur due to acetylcholine receptor antibodies, muscarinic receptor three antibodies, different sorts of nerve damage, and/or secondary metabolic muscle issues (Bengtsson et al., 2011; Pierce et al., 2016). Celiac disorder has been referred to in around 15% of the SS subjects as well as other several food hypersensitivities (Barton & Murray, 2008; Pittman & Holub, 1965). Several SS subjects were defined to involve inflammatory bowel diseases (Gainey et al., 1985). Exocrine dysfunctioning in pancreas has been noted in 18%–37% of 'primary SS cases. However, chronic or acute pancreatitis is reported in about 0%–7% of the SS patients. There are generally no liver diseases associated with primary SS. Nonetheless, secondary SS may be recognized in relation with numerous autoimmune liver ailments inclusive of primary sclerosing cholangitis, autoimmune hepatitis and primary biliary cirrhosis (Floreani et al., 2014). Moreover, hepatitis C infection is not merely related with

keratoconjunctivitis sicca however additionally among the autoantibodies demonstrated in primary SS patients (Buskila, 2009).

Neurological manifestations in SS can include both the central and peripheral nervous system and can be the describing signs in numerous patients. Peripheral nervous system manifestations integrate sensorimotor neuropathy, sensory neuropathy, involvement of cranial nerve, polyradiculoneuropathy and mononeuritis multiplex (Mellgren et al., 2007). Central nervous system (CNS) presentations engross transverse myelitis, meningitis, encephalitis, stroke, seizure, vasculitis, disorder like multiple sclerosis, and numerous psychiatric and cognitive abnormalities (Massara et al., 2010). The mechanisms of nervous system injury in SS remains indefinable however may encompass numerous overlapping physiological courses. There might be autoantibodies disturbing nervous system functioning, like aquaporin four antibodies which have been related to the multiple sclerosis-like disorders including the cerebrum, optic nerve, spinal wire and brainstem (Dellavance et al., 2012).

The vascular device is usually complicated in SS patients. The most general complication is Raynaud's, taking place in 30%–50% of the SS patients (GarciaCarrasco et al., 2002; Kraus et al., 1992). Besides causing brief coloration adjustments observed in the hands and toes, Raynaud's may lead to reversible vasospasm of CNS, migraine and brief ischemic episodes, reversible pulmonary hypoxemia, stomach and Prinzmetal's angina (Gupta et al., 2014). Raynaud's may also or may not be related with the incidence of antiphospholipid antibodies (Cervera et al., 2002). The occurrence of lymphoma is elevated in various autoimmune disorders, but most drastically in SS. The prevalence of lymphoma in primary SS individuals has been noted to be between 5% and 10% (Voulgarelis et al., 2012; Zintzaras et al., 2005). The malignancies associated with SS are usually non-Hodgkin's B-cell lymphomas that may be diverse histological subtypes together with large B-cell lymphoma (LBCL), follicular lymphoma and marginal quarter lymphoma (Smedby et al., 2008). The tumors interestingly, may not only initiate inside the salivary glands but additionally in other several mucosal lymphoid tissues, like the Peyer's patches, indicating that there may be systemic dysfunctioning of the B cells. Very little is understood concerning the progression of the chronic inflammation into lymphoma, but the rapid autoreactive cell proliferation result in accumulation of aberrations that in the long run lead to malignant state. Another speculation is that there is intrinsic abnormality within the B cells of SS individuals that cause malignant cells to progress after additional environmental stimulus (Mackay & Rose, 2001).

SS is considered as an autoimmune disease due to the fact that organ injury is described in the appearance of autoantibodies and in the nonappearance of other descriptions for the organ injury. Autoantibodies, including anti-Ro, which might be used to outline SS as a disease entity, may additionally have many functional roles as well. Research in diverse autoimmune disorders have supported that few autoantibodies, specifically IgM autoantibodies, can be used by the immune system to distinguish injured

tissues and produce cells which could take part in damaged tissue repair (Gronwall & Silverman, 2014).

2.3 Systemic sclerosis

Systemic sclerosis (SSc), previously known as scleroderma is an autoimmune disorder affecting connective tissue with multifarious and poor implicit etiology. SSc has fluctuating medical difficulties, follows a continual and generally progressive column, and is linked with appreciably reduced quality of life, mortality and disability. Besides involvement of skin, the characteristic of the disorder, practically every tissue may be implicated.

SSc indicates marked person-to-person irregularity in its modes of skin inclusion, disease advancement, autoantibody titer, survival and response to remedy (Allanore et al., 2015). SSc is ordinarily distinguished into moderately overlapping subsets which might be defined along with serological and clinical functions with the course of skin inclusion. Patients having diffused cutaneous SSc (dcSSc) often and extensively have skin indurations progressively rising from distal fingers (sclerodactyly) up to the proximal extremities (over knees and/or elbows) including trunk. Acute scleroderma renal disorder and interstitial lung disease (ILD) also develop in these individuals comparatively at the beginning of the disorder. Limited cutaneous SSc (lcSSc) in contrast, tends to be slow and is featured by Raynaud's phenomenon prior to other complications, at times by years. The skin indurations in lcSSc, exhibit slow development and remains constrained to the face, distal limbs and fingers. Many individuals having lcSSc show a typical collection of clinical features like calcinosis cutis, esophageal dysmotility, Raynaud's phenomenon, mucocutaneous telangiectasia) and sclerodactyly, that result in the CREST syndrome designation. Nonetheless, CREST manifestations may as well be featured in dcSSc patients. On contrary to dcSSc, involvement of visceral tissues in lcSSc tends to observe a languid pattern, with pulmonary arterial hypertension (PAH) and digital ischemic ulcers as late symptoms. Some persons may manifest Raynaud's phenomenon together with specific medical, serological and capillaroscopic characteristics of SSc with no visible skin induration (sine scleroderma).

The latest epidemiological European study noted an incidence of 228 cases per million in the Alsace area of France (Meyer et al., 2016). SSc appears to be much less prevalent in Asia. SSc has woman predominance with maximum approximates of female-to-male ratios varying from 3:1 to 9:1 [reviewed in Chifflot et al. (2008)]. In a large European SSc database (EUSTAR) 86% of the cases have been females (6.2:1 ratio) (Meier et al., 2012). The high proportion of women in SSc is just like other autoimmune rheumatic disorders like rheumatoid arthritis and systemic lupus erythematosus. The reason for female predominance remains elusive however, pregnancy associated episodes and hormonal effects have been proposed. It is also postulated that microchimerism may cause female preponderance of SSc. Microchimerism takes place while during pregnancy

there is a transfer of cells between fetus and mother that results in the perseverance of genomically isolated host cellular populations (Bianchi et al., 1996). An alternative cause of woman dominance in SSc is the subjective X-chromosome inactivation in the direction of one parental supply, main to a digression from the speculative inactivation ratio1:1 (Kanaan et al., 2016). SSc is linked to a considerable extra mortality. A metaanalysis of nine researches carried out between 1960 and 2010 determined a collective standardized mortality ratio (in comparison to the gender and age-matched preferred population) of 3.53 (Elhai et al., 2011), which become higher in comparison to standardized mortality ratio in other various autoimmune rheumatic disorders (Toledano et al., 2012). Environmental elements are also contemplated to play functional part in SSc etiology. Occupational exposure to silica is considered as potential environmental trigger of SSc. A metaanalysis of 16 unique investigations depicted that exposure to silica increases the chance for SSc, mainly in male patients (McCormic et al., 2010).

The composite etiology of SSc displays a distinctive triad of pathomechanistic courses that is infection/autoimmunity (van den Hoogen et al., 2013), fibrosis in various organs (Leroy et al., 1980) and microangiopathy (Allanore et al., 2015). The relative degree of severity and involvement of these three intricate pathomechanistic courses to the general disease activity and clinical scenario fluctuate among cases and through disease course over the years (Gabrielli et al., 2009). Inflammation, autoimmunity and distorted vascular activity ensue at the beginning of disorder and, consequently, result in fibrosis, atrophy and vascular loss in various tissues.

SSc is regarded as a polygenic disorder related to numerous genetic vulnerability loci, each with low-to-slight effect size. The aggregate of stochastic and environmental elements gathering upon cases of selected genomic conditions appear to eventually result in disease progression. The advent of GWAS and large-scale global associations have noticeably stepped forward our knowledge of genetics regarding SSc. Whereas the most powerful disease associations have been discovered inside the HLA and around 20 vulnerability loci outside the HLA area have also strongly been related to SSc. The popular SSc risk genes are assumed to be implicated in immune reactions and are likewise vulnerability loci for systemic lupus erythematosus and various other autoimmune disorders (Martin et al., 2012). The powerful associations in GWAS have been reported on chromosome six inside the class II of HLA area. These findings offer a necessary support for the opinion that SSc is essentially an autoimmune disorder.

Vascular injury is generally an early incident playing a prime role in SSc etiology. Extensive harm in numerous vascular beds develops and underlies erratic physiological descriptions of SSc. The medical microangiopathic sequelae of SSc involve ischemic virtual ulcers and Raynaud's phenomenon, watermelon belly, scleroderma renal crisis, mucocutaneous telangiectasia, myocardial inclusion and PAH (Matucci-Cerinic et al., 2013). Raynaud's phenomenon is the most regular clinical, extracutaneous expression of SSc. It is described by incidence of reversible vasoconstriction in the toes and fingers,

often impacting the earlobes and nose tip. Symmetrical bilateral thickening of skin is the distinguishing feature of SSc that differentiate it from other connective tissue disorders. Pruritus is a regularly occurring expression and is related to reduce apparent health (El-Baalbaki et al., 2010). PAH and ILD are the two foremost variety of pulmonary involvement in SSc, and the main reasons of disease-related mortality (Tyndall et al., 2010). Gastro intestinal (GI) track involvements develop in as much as 90% of the cases with SSc and are similarly prevalent in lcSSc and dcSSc. GI difficulties lead to malnutrition, fatigue, high mortality and reduced quality of life (Tyndall et al., 2010). A chief complication of SSc is Scleroderma renal crisis which once was a main cause of mortality in the era of preangiotensin changing enzyme (ACE) inhibitor. The complication of high blood pressure accompanied through progressive failure develops in about 5%–15% of the individuals, and nearly occurs consistently within 4 years of disease inception (Penn et al., 2007).

SSc is related to quite definite autoantibodies, which up to now are the best potential markers predicting definite organ expressions. Autoantibodies specific to SSc have a tendency to be collectively different and distinctly unique (Arora- Singh et al., 2010). However, various collections of antibodies may be detected whilst determined through novel multiplex tests (Mehra et al., 2013). The clinical significance of SSc-autoantibodies is emphasized by the concept that incidence of ATA anti-RNA polymerase III (RNAP), or ACA antibodies is incorporated in the European League Against Rheumatism Classification Criteria/American College of Rheumatology 2013 (van den Hoogen et al., 2013).

Around 96% of patients with SSc are ANA positive. SSc patients who are negative for ANA experience much less vasculopathic difficulties (such as telangiectasia, PAH, ischemic virtual ulcers) and are more prone to engross GI complications (Salazar et al., 2015). ATA (additionally known as anti- Scl-70) antibody is more prevalent amongst Asian and Black patients, and is related with diffuse cutaneous manifestations and elevated possibility for developing progressive ILD (Nihtyanova et al., 2014; Steen, 2005; Steen et al., 2012). ACA, on contrary more frequent in whites, is related to limited cutaneous manifestations, though clinically considerable ILD is unusual and survival rates are higher. ACA is likewise related to calcinosis and co incidence of biliary cirrhosis (Assassi et al., 2009; Nihtyanova et al., 2014; Steen et al., 2012).

2.4 Spondyloarthritis

The spondyloarthritis (SpA) disorder include axial spondyloarthritis (axial SpA) which include ankylosing spondylitis (AS), reactive arthritis (ReA), arthritis/spondylitis with psoriasis and arthritis/spondylitis with inflammatory bowel disease (IBD). The chief association between each one of these are the relation with HLA-B27, related pathological signs, along with inflammatory back ache, and comparable manners of secondary joint

manifestations with a non symmetric arthritis primarily of the lower limbs, and high possible incidence of spondylitis, sacroiliitis, uveitis and enthesitis. Spondylitis ankylosans is also known as Morbus Bechterew or Bechterew-Strümpell-Marie sickness. Its incidence has been assessed to be between 0.2% and 0.9% and the disorder is usually incepted in the second decade of life. The recent estimation of male to female ratio is about 2:1. 90%–95% of cases are found to be positive for HLA-B27 and psoriasis, inflammatory bowel sickness, or previous ReA may be determined in around 10% of the individuals with AS. Back ache is the main clinical feature in axial SpA cases and is illustrated by morning stiffness which subsides by workout. This disorder occurs in over 90% of patients with sacroiliitis. Furthermore, the entire spine may be implicated with arthritis, spondylitis and spondylodiscitis of the little intervertebral joints with the course of disease. Laboratory findings for disease diagnosis include CRP, HLA-B27 assessment and positive imaging. Sacroiliitis on X-rays (structural injury) or on MRI (inflammation) are critical for the diagnosis and classification of axial SpA (Rudwaleit, Jurik, et al., 2009; Rudwaleit, van der Heijde, et al., 2009). ReA occur after intestinal infection with enterobacteria like Salmonella, Yersinia, Shigella, Campylobacter jejuni or urogenital tract infection with Chlamydia trachomatis, generally only after some time as much as 4–6 weeks (Sieper et al., 2000). MRI assisted studies have proven that in SpA the most applicable site for inflammatoion is osteitis at the interface of bone/cartilage (McGonagle et al., 1999). Osteitis is noticed in short-tau inversion recovery pattern and suggests a homeostatic alteration of the bone marrow. Osteitis in the ilium and sacrum close to the sacroiliac joints is a common observation in axial SpA (Rudwaleit, Jurik, et al., 2009; Rudwaleit, van der Heijde, et al., 2009). Persistance of disease for a long time might also cause structural modifications inside the subchondral bone, such as ankylosis, narrowing of joint space and erosions, which may be observed using X-ray. Osteitis inside the spine may be noticed especially at the vertebral body ends where development of syndesmophyte is observed with the course of time (Baraliakos et al., 2014).

Instead of the presence of distinct autoantigen, bacterial exposure of immune system seems to be crucial for triggering SpA. It is fairly evident from ReA, which is prompted generally by infection of genitourinary tract with C. Trachomatis or enteritis. Within the synovium microbial presence indicate that ReA could develop due to the incidence of microbial immunogens at inflammatory arthritic sites (Granfors et al., 1989). Around 20%–40% of the ReA patients with HLA-B271 manifests the whole clinical features of AS after 10–20 years (Leirisalo-Repo, 1998). Even though clinically identified ReA is estimated to precede AS in much less than 10% of the occurrences, this figure might be more due to the fact that most of the infections of gut or urogenital tract are generally asymptomatic. The AS propensity has been assessed to be higher than 90% genetically distinctive, thus a ubiquitous environmental factor has also been suggested. HLAB27 is the most applicable genetic component (Brewerton et al., 1973). The relation of HLA-B27 with SpA is considered the best acknowledged MHC association for any

human disease and the most precise aspect for SpA etiogenesis. Other MHC genes, besides HLA-B27, including HLA-DR1 and HLA-B60, are also thought to be related, yet with little significance. However, despite the fact that MHC is regarded as the fundamental vulnerability locus, it is recommended that its contribution is merely about 36% to the entire genomic risk (Brown et al., 2002).

Only a little fraction (1%–5%) of carriers of HLA-B27 develop AS, which could not be elucidated by HLA-B27 subtypes. Since we understand from unbiased twin study that the genetic AS propensity is above 90% (Brown et al., 1997), it is most probable that different genes make a contribution to the vulnerability. In addition GWAS in past few years have recognized a precise association of AS with the non-MHC genes IL-23R and ERAP1 and also with the gene deserts 21q22 and2p15 (Australo-Anglo-American Spondyloarthritis Consortium (TASC) and Wellcome Trust Case Control Consortium 2 (WTCCC2), 2011; Welcome Trust Case-Control Consortium and Australo-Anglo-American Spondyloarthritis Consortium, 2007).

2.5 Rheumatoid Arthritis

Rheumatoid Arthritis is the most frequent chronic joint inflammatory disease, estimated to affect 0.5%–1% of the population in the developed world and women are more susceptible than males (2–3:1) (Eriksson et al., 2013; Helmick et al., 2008; Silman & Pearson, 2002). However, the prevalence figure is much high in certain population of Native America (Eriksson et al., 2013) populations (Helmick et al., 2008). The etiology of the disease remains unknown; however, various evidential factors indicate that both genetic as well as environmental elements contribute to pathogenesis. Various environmental risk elements regarding etiology were recognized:

(1) RA has been considered as a sickness of the poor since its description (Landre-Beauvais, 1800) and people with low socioeconomic background and low awareness are more afflicted with adverse inflammation and RA (Callahan & Pincus, 1997; Packard et al., 2011; Uhlig et al., 1999);

(2) Smoking might elevate RA risk and severity and is linked with higher generation of autoantibody and tumor necrosis factor (TNF) which is linked in turn with genetic features specific to RA (Glossop et al., 2006; Mattey et al., 2002; Silman et al., 1993; Symmons et al., 1997; Uhlig et al., 1999), while these relations are yet to be proved in whole populations (Klareskog et al., 2011; Vesperini et al., 2013);

(3) The microbiota, particularly within the GI tract, has also been recognized as a critical autoimmunity controller and seems to play an essential part in experimental modes of arthritis (Abdollahi-Roodsaz et al., 2008; Wu et al., 2010; Yoshitomi et al., 2005).

In humans, RA has been associated with bacterium like Porphyromonas gingivalis, which produces an enzyme peptidyl-arginine deiminase (PADI) that catalyze citrullination (Scher et al., 2012; Wegner et al., 2010). Prevotella copri has recently been

connected to the RA etiology, as this bacteria is over extended in RA cases where both cellular and humoral immune reaction against this microbe has been found (Pianta et al., 2017; Scher et al., 2013). Hormonal elements besides other aspects might also contribute to the RA progression (Silman & Pearson, 2002).

The foremost pathological characteristic feature of RA is pain and swelling in the joints. According to 2010 ACR/EULAR classification criterion, clinical synovitis (Aletaha et al., 2010), which can be used specially for scientific trial processes however also can guide the diagnostic procedure, involve the incidence of scientific synovitis (swelling because of synovial complications) in at least one joint. Joints concerned are generally those of the fingers, wrists, knees and toes (Smolen et al., 1995) however additionally various other joints may be implicated, while few joints, together with the distal interphalangeal joints, are generally protected. In RA, visibly swollen Joints not only feel pain upon movement but also develop tenderness to low pressure and become rigid for hours after long rest like in the morning. Synovitis results in erosions of subchondral bone and cartilage injury and hence the RA pathology which can lead to entirely destructed joints, as clinically visible upon radiograph imaging.

RF and ACPA are the most frequent autoantibodies seen in RA and are essential for diagnosis and classification criteria (Aletaha et al., 2010). Their specificity and sensitivity for the diagnosis of RA are almost equivalent (specificity about 85%–95%, sensitivity around 50%–60%) (Mjaavatten et al., 2010; Neogi et al., 2010; Nicaise-Roland et al., 2013). Although these two autoantibodies vary with the disease course and efficient remedy, but RF appear to fluctuate comparatively to a higher degree (Bohler et al., 2013); in fact, with long-standing remission it can turn negative (seroconversion), such is not regarded for ACPA. ACPA may be assessed for utilizing various kinds of citrullinated antigens like as fibrinogen, filaggrin, CII, vimentin, cyclic peptide or enolase. These autoantibodies slightly differ in terms of period of appearance and incidence (Brink et al., 2013; Nicaise-Roland et al., 2013). An additional autoantibody is anti-RA33, which may be specified for diagnosis, particularly if ACPA and RF are found negative (Nell et al., 2005).

All mentioned autoantibodies especially ACPA, also can be found in multiple diseases, particularly several infectious and autoimmune disorders (Abdel Fattah et al., 2009; Bassyouni et al., 2009; Gokhan et al., 2013; Lima & Santiago, 2010; Singh et al., 2011). These can as well be seen in normal individuals as it was earlier suggested that RF positivity enhances with age, however this is irrelevant as per recent investigations (Nielsen et al., 2012). ACPA and RF are considered as novel autoantibodies of RA and prove to be more effective in the diagnostic criteria of the disorder (Aletaha et al., 2010). The exact pathophysiology of the disease expression is nevertheless insufficiently understood. It is now believed that antigen presenting cells takes up autoantigen or unidentified foreign antigen, that via specific antigen presentation and costimulation result in adaptive and innate immune activation. The presence of the mutual epitope

implies that either mainly arthritogenic peptides get bound to these with high affinity and not other MHC component or that a T-cell arthritogenic repertoire is chosen by means of the mutual epitope. The activated T cells, which are insufficiently controlled by regulatory T cells (Chavele & Ehrenstein, 2011), prompt macrophages and assist B-cells that ultimately results in inflammatory cell influx into the synovial membrane; this inflammatory synovial membrane now get transformed into an autonomous tissue called pannus which is "semimalignant" leading to bone and cartilage destruction. Infact, the most unique feature of RA that distinguishes it from different inflammatory diseases is the excessive predisposition for joint damage. Cartilage injury is supposed to appear due to either metalloproteinases activity on cartilage matrix formed in the joint and/or through the chondrocyte activity via cytokines with consequent damage to matrix; here, the synovial membrane connection with the cartilage is assumed to play a critical role in this respect (Korb-Pap et al., 2012).

Bone damage is interceded by activated osteoclasts inside the synovial membrane at points adjoining bone (Gravallese et al., 1998; Redlich et al., 2002). Indeed, the incidence of RF has been implicated in the joint injury via the interaction with advanced disease activity and also independently of disease activity (Aletaha et al., 2013).

2.6 Juvenile idiopathic arthritis

Juvenile idiopathic arthritis (JIA) is an exclusion diagnosis which combines all arthritic types with indefinite basis. Its onset is before the age of 16 years which last for more than 6 weeks (Prakken et al., 2011; Ravelli & Martini, 2007). JIA is the multifaceted collection of chronic arthritides integrated by the manifestation of chronic inflammatory processes, chiefly involving the synovial membrane. The long term membrane inflammation might elevate the risk for osteocartilagineous destruction with subsequent structural disability. The pathogenesis of JIA remains unknown however, its heterogeneity suggests that diverse elements are probably involved in its pathogenesis. JIA is regarded as the most frequent chronic rheumatic state in childhood and an essential reason for long term as well as short term disability. Even though present world over, the prevalence and incidence of JIA varies drastically all through. Studies from Western populations have shown an incidence changing respectively from 2 to 20 and from 16 to 150 per 100,000, being high prevalent in northern Europe (Ravelli & Martini, 2007). The umbrella term of JIA cover several distinctive varieties of chronic arthritis including Systemic JIA (sJIA), Oligoarthritis, Enthesitis-Related Arthritis, Undifferentiated Arthritis, Psoriatic, Rheumatoid Factor Positive and Rheumatoid Factor Negative Polyarthritits,. Systemic JIA (sJIA) is regarded the most severe inflammatory disease of childhood accounting for 10%–15% of the children having JIA. s JIA first defined by Sir George Frederic, is categorized by arthritis and distinguished systemic manifestations including high-spiking fever, hepatosplenomegaly, an transient pink rash of skin that often occurr with high fever

peaks, serositis and general lymphadenopathy. During fever peaks there may be myalgias and abdominal pain. Around 5%–8% of the children is known to develop macrophage activation syndrome (MAS), a life threatening manifestation (Ravelli et al., 2012). The distinguishing feature of MAS is dysregulated immune activation including the persistent activity of T lymphocytes and macrophage expansion resulting in a real cytokine storm. The disorder is a kind of reactive hemophagocytic lymphohistiocytosis (HLH) and there is unexpected sustained fever onset, hepatosplenomegaly, pancytopenia, coagulopathy, liver insufficiency, neurological symptoms and hemorrhagic complications. sJIA perhaps does no longer constitute a disease but instead a syndrome, with each disease inflicting a persistent and marked innate immune activation (Martini, 2012a, 2012b). sJIA is found more common in children in comparison to adults, where it is known as adult-onset Still's disorder. This refers to a role for several extensively subtle infectious elements which can be encountered in early life or signifies the impact of robust genetic predisposed conditions. The syndrome is often regarded as multi factorial and polygenic, even though it is not recognized if the genetic disposition is because of the grouping of usual gene variants, with each imparting a little sJIA contribution to inborn vulnerability, or to excessive-penetrance unusual aberrations that simply account for a few instances each.

It is clearly evident from laboratory investigations and remedial efficiency that phagocyte-derived cytokines particularly IL-6 and IL-18, and IL-1 play a chief role in sJIA etiology. Circulating IL-6 levels are notably elevated, and are correlated with platelet number and the degree and severity of joint complications (De Benedetti et al., 1991). IL-6 levels in synovial fluid also are markedly higher and considerably increased as compared to the individuals with RA or oligoarticular and polyarticular JIA (De Benedetti, Alonzi, et al., 1997; De Benedetti, Pignatti, et al., 1997). The most convincing proof for the imperative role of IL-1 in sJIA etiology appeared from the pretty serendipitous detection of the distinct remedial efficiency of an IL-1 inhibitor, anakinra that is the recombinant model of the natural antagonist of soluble IL-1 receptor (Pascual et al., 2005; Verbsky & White, 2004). In addition both sJIA, and adult-onset Still's disease, are categorized by means of elevated circulating IL-18 levels (Kawashima et al., 2001; Maeno et al., 2002).

2.7 Antiphospholipid syndrome

Antiphospholipid syndrome is an autoimmune disorder, mediated by autoantibodies that are driven against phospholipids and phospholipid-associated proteins. Antiphospholipid antibodies (aPL) are identified in around 1%–5% of the general population, however minor number of aPL-positive persons develop APS. The prevalence of APS is predicted to be about 40–50 cases per 100,000 persons (Cervera, 2017). Secondary APS is predicted to arise in 10%–15% of subjects with SLE and much lesser in different autoimmune

disorders. In contrast with healthy aPL-positive normal controls, cases having either primary APS or secondary APS manifest typically with continual (>12 weeks), high-range aPL seropositivity and considerable connected mortality and morbidity (Cervera et al., 2009). Catastrophic APS (CAPS) is very uncommon and is implicated in <1% of all APS subjects (Asherson et al., 2003). APS diagnosis is made following thrombotic or obstetric morbidity. Nevertheless, the clinical sphere of APS nowadays is considered to be broader including organ-specific and systemic manifestations brought on via both immune-mediated and thrombotic pathways (Marai et al., 2004; Shoenfeld, 2007). Additionally, a huge array of clinical appearances may additionally rise up because of occlusions in single or various vessels.

The most common APS manifestations as per the Euro-Phospholipid Project include

1. Peripheral thrombosis including deep vein thrombosis (38.9%), Superficial thrombophlebitis (11.7%) and arterial thrombosis in legs (4.3%), venous thrombosis (3.4%) and arterial thrombosis in arms (2.7%), subclavian (1.8%) and jugular vein thrombosis (0.9%).
2. Neurologic manifestations including migraine (20.2%), Stroke (19.8%), Transient ischemic attack (11.1%), Epilepsy (7.0%), Multiinfarct dementia (2.5%), Chorea (1.3%), Acute encephalopathy (1.1%).
3. Pulmonary manifestations: Pulmonary embolism (14.1%), pulmonary hypertension (2.2%), Pulmonary microthrombosis (1.5%).
4. Cardiac manifestations: Valve thickening/dysfunction (11.6%), Myocardial infarction (5.5%), Angina (2.7%), Myocardiopathy(2.9%), Vegetations (2.7%), Coronary by-pass rethrombosis (1.1%).
5. Renal manifestations: glomerular thrombosis, renal infarction, renal artery thrombosis, renal vein thrombosis (2.7%).
6. Gastrointestinal manifestations: esophageal or mesenteric ischemia (1.5%), Splenic infraction (1.1%).
7. Cutaneous manifestations: Livedo reticularis (24.1%), Ulcers (5.5%), Pseudovasculitic lesions (3.9%), Digital gangrene (3.3%), Cutaneous necrosis (2.1%).
8. Osteo-articular manifestations: Arthralgia (38.7%), Arthritis (27.1%), Avascular necrosis of bone (2.4%).
9. Ophthalmologic manifestations: Amaurosis fugax (5.4%), Retinal artery thrombosis (1.5%).
10. E.N.T. manifestations: Nasal septum perforation (0.8%).
11. Hematological manifestations: Thrombocytopenia (˂100,000 per μL) (29.6%), Hemolytic anemia (9.7%).
12. Obstetric manifestations: Preeclampsia (9.5%), Eclampsia (4.4%), Abruptio placentae (2.0%), Fetal manifestations, Early fetal losses ˂10 weeks) (35.4%), Late fetal losses (≥10 weeks) (16.9%), Live births (47.7%), Prematures (10.6%).

Obstetric manifestations including maternal and fetal are a hallmark of APS and in recent times are identified as a separate matter from vascular APS. Early recurrent pregnancy losses (˂10 weeks of gestation) take place in around 1% of the regular obstetric populations and 15% among them are linked to APS. Difficulties regarding fetuses in patients with obstetric APS (OAPS) involve intrauterine growth limit because of placental insufficiency, prematurity, and late and early pregnant losses. Fetal losses are regarded as the characteristic feature of OAPS, and the presence of antiphospholipid antibodies has strongly been associated with the fetal loss (Abou-Nassar et al., 2011; Silver et al., 2013). Preeclampsia is the most common maternal expression found in APS, following abruption placentae and eclampsia. Arterial and/or venous thrombosis are exclusive features of APS (Taraborelli et al., 2012), and vessels of any length and at any site can be implicated (Saponjski et al., 2011). These thrombotic instances are the chief cause of mortality and morbidity in APS, and that they likely reappear predominantly in untreated individuals (Taraborelli et al., 2012). Catastrophic Antiphospholipid Syndrome (CAPS) is categorized by extensive intravascular thrombosis in a brief time period that results in malfunctioning of multiple organs (Carmi et al., 2017). CAPS typically involve numerous small size vessels, but along small ones big vessels sometimes may also be occluded (Erkan et al., 2010). aPL include a collection of around 30 distinct autoantibodies directed toward a broad range of antigens like phospholipid-binding proteins, negatively charged phospholipids, and components linked to hemostasis (de Groot et al., 2012). The modified clinical classification criteria regarding APS however involve only Lupus Anticoagulant (LAC), anticardiolipin (aCL), and Anti-b2-Glycoprotein-I Antibody (anti-B2GPI antibodies) (Miyakis et al., 2006). Besides, other antibodies such as Antiphospholipid Antibodies of the IgA Isotype, Autoantibodies to Domain one of b2-Glycoprotein-I (anti-B2GPI antibodies), Antiphosphatidylethanolamine (aPE) antibodies, Antiphosphatidylserine (aPS), Antiprothrombin antibodies (aPT), Anti phosphatidylserine/prothrombin (aPS/PT), Antiannexin A5 Antibodies have also been demonstrated in patients with APS.

The latest information suggests the presence of a genomic component in APS, each as primary or in affiliation with SLE. The genetic component is somewhat related to the HLA complex, and various kin research have proven that haplotypes, specifically those holding DRw53 and DR4, might be linked with aPL formation or APS itself (reviewed in Sebastiani et al., 2016). Moreover, epigenetic activities such as histone modification, nucleosome transforming, noncoding RNA, and DNA methylation offer advanced insights with regard to APS (Zhang & Zhang, 2015). The pathogenic outcomes of aPL are exerted via binding of specific antibodies to the receptors on target cells like endothelial cells, trophoblasts, and monocytes which results in consequent interruption of intracellular signaling pathway (Blank et al., 1991; Giannakopoulos & Krilis, 2013).

Various mechanisms were suggested regarding thrombosis development, such as the stimulation of monocytes, endothelial cells, platelets, complement and coagulation pathways, in addition to the prevention of anticoagulation and fibrinolytic processes (Merashli

et al., 2015). The mechanisms with regard to aPL-related obstetric complications include inflammation, intraplacental thrombosis, defective annexin A5 function, preclusion of syncytium-trophoblast differentiation, placental apoptosis/disruptive placentation, and complement activation (reviewed in Arachchillage et al., 2017). Inflammation is proposed as one of the predominant course of aPL-related pregnancy morbidities, and it has received extra support from a recent in vitro analysis showing that aPL could result in interleukin-1β by inducing trophoblasts via inflammasome stimulation (Mü ller-Calleja et al., 2015). Complement system has apparently been implicated in APS since antibodies could not apply their immunogenic impact in animals lacking complement elements. This impact has been reported in both thrombosis model (Fischetti et al., 2005) and pregnancy losses (Holers et al., 2002). The implication of complement system in pregnancy morbidities related to APS individuals is additionally supported by way of histopathological assessment of placentae in females with aPL (Viall & Chamley, 2015).

2.8 Autoimmune myopathies

The autoimmune myopathies involve unusual spectrum of diseases, integrated via autoimmune skeletal muscle injury (Mammen, 2011). These can appear as a distinctly featured disease like polymyositis (PM), immune-mediated necrotizing myopathy (IMNM) and dermatomyositis (DM) or as a characteristic of different systemic autoimmune disorders like scleroderma or systemic lupus erythematosus. Although skeletal muscle is considered as a principal target in the autoimmune myopathies, often there are various other organs which could additionally be affected, like skin, synovial joints, lungs and cardiac muscles. Autoimmune myopathies alike most other autoimmune rheumatic disorders, are very complex in their clinical setup. These disorders are usually categorized by the inception of weakness without pain, affecting in particular proximal muscle tissue symmetrically (Christopher-Stine et al., 2012; Miller, 2012; Robinson & Reed, 2011). The striated muscles of the top esophagus and nasopharynx may also be involved in few cases, with nasal regurgitation, disruptive phonation, issue in swallowing and propensity to aspiration.

In extreme instances, weakliness of the breathing muscles may also occur, however this is very rare. Muscle complications occur by means of the discharge of several muscle enzymes like creatine kinase, alanine and aspartine transaminases, additionally aldolase A which can be mistakenly inferred as liver dysfunctioning. Furthermore, the inflammatory myopathies are featured on electromyography by irritable myopathy.

Skin complications are prominent descriptions in dermatomyositis, with the skin type and pattern being used for diagnostic purposes. Typical dermatological symptoms include:

(1) facial heliotrope rash across the eyelids;
(2) Gottron's papules, inflammatory flaking papules restricted to the dorsal metacarpophalangeal and proximal interphalangeal joints;

(3) a vicious eruption related to the shawl region, chest, thighs and flanks

(4) palmar papules and skin ulcers, occurring in a definite sub population of individuals with dermatomyositis (Chaisson et al., 2012). There is perifascicular inflammatory atrophy and regeneration in dermatomyositis while polymyositis is featured via intrafascicular inflammation and regeneration as is being evident from lymphocytes seen around normal muscle tissue. In comparison, there is a confined inflammatory infiltration in immune-mediated necrotizing myopathy. While necrotic muscle tissues are described in both dermatomyositis and polymyositis, they're fairly loaded in necrotizing myopathy. There is a rising admiration that clinical presentation in any particular individual is often indistinctive, with descriptions of the typical entity found in varied combinations (Pestronk, 2011). The autoantibodies implicated in myositic patients recognize a group of autoantigens having essential, reserved functions like gene expression, protein translation, post translational modifications, DNA repair mechanism, exosome complex and formation of nuclear bodies (Casciola-Rosen et al., 1995, 2001; Mathews & Bernstein, 1983; Mimura et al., 2010; Okuma et al., 1999; Reeves et al., 1986; Suwa et al., 1996; Targoff & Reichlin, 1985).

2.9 Immunoglobulin G4-related disease

Immunoglobulin G4-related disease (IgG4-RD) is an immune-mediated fibroinflammatory disorder that affects multiple tissues with a collection of organ-specific effects. Even though various single tissue complications had been described long ago, its systemic features and distinctive characteristics were only recently found when IgG4-RD appeared as a distinct disease entity. IgG4-RD involves several single-organ manifestations once believed as rare isolated diseases including eponymous syndromes, such as Küttner's tumor, retroperitoneal fibrosis (RPF), autoimmune pancreatitis (AIP), Riedel's thyroiditis, Sclerosing cholangitis, Mikulicz's disorder, Multifocal fibrosclerosis, Mediastinal fibrosis, Sclerosing mesenteritis, Retroperitoneal fibrosis, Periaortitis/periarteritis, Hypertrophic pachymeningitis, Inflammatory aortic aneurysm, Eosinophilic angiocentric fibrosis, tubulointerstitial nephritis.

The epidemiology and organ presentations of IgG4-RD are generally regarded to be very rare. IgG4-RD was originally identified in pancreas. Type 1 (IgG4-related) AIP was predicted to have an overall prevalence of 2.2 cases per 100,000 people in Japan (Kanno et al., 2012), although this estimate obviously understates the true incidence because the study was carried out very recently after the first publications describing the disorder. An adult male between middle age and old is the usual patient with IgG4-RD. Although there have been a few unusual pediatric cases reported, the average age at diagnosis for AIP is around 67 years (Griepentrog et al., 2013). The majority of studies show an overall preference for men, particularly for IgG4-related pancreatitis with a Male:Female ratio of 3:1 (Kanno et al., 2012). However, when all IgG4-RD organ involvement types are

taken into account, this ratio may be closer to 3:2. In contrast to the typical autoimmune disorders, the disease is considerably less frequent in women, but it does not seem to be any less severe in females (Wallace et al., 2015). However, women may experience sialadenitis and dacryoadenitis linked to IgG4 more frequently (Inoue et al., 2015).

Additionally, despite recent developments in the detection of the basic immunological pathways, the pathophysiology of the condition is still not entirely understood. Plasmablasts and activated B cells from the B lymphocyte lineage interact with at least two CD41 T lymphocytes, CD41 T follicular helper cells, and a CD41 CTL in IgG4-RD (Perugino et al., 2019). CD41 CTL is presently believed to be the linchpin of the disorder as these are plentiful in IgG4-RD tissues, clonally confined, and possibly contribute to fibrosis through various mechanisms, including the release of profibrotic cytokines like interleukin (IL)-1β, IL-4, IL-10,1L-13, transforming growth factor-beta (TGF-β), and interferon-gamma (IFN-γ). TGF-β and IL-13 may cause fibrosis by activation of fibroblasts, while IL-10 and IL-4 are believed to promote the IgG4-specific class-switch recombination in B-lymphocytes (Della-Torre et al., 2015; Tsuboi et al., 2012) and apoptosis induction in target cells (Mattoo et al., 2016). IgG4-RD tissues frequently include up to 80% of all invading CD41 T cells, and CD41 CTLs appear to be present in all IgG4-RD patients. The gene profile of the CD41 CTL seen in IgG4-RD include cytolytic (like perforin granulysin and granzyme) as well as myeloid (like IL-1β) characteristics. It is hypothesized that active B lymphocytes may have an essential role in the IgG4-RD pathogenesis as these cells trigger the CD41 CTL activation at the disease sites via antigen presentation and B-cell diminishing therapy with rituximab, anti-CD20 monoclonal antibody results in both substantial clinical responses and reductions in CD41 CTLs (Perugino et al., 2019).

IgG4-RD involves a complicated diagnostic process that often combines clinical assessment, imaging, serological and histological analysis. However, no single investigation is exclusive to IgG4-RD. Therefore, a thorough interpretation of the examination finding in context with clinical presentation of patient is necessary for its diagnosis and the exclusion of a wide range of differential diagnosis as well. The main diagnostic criterion for IgG4-RD was once believed to be serum IgG4 levels (Hamano et al., 2001). However, it immediately became apparent that increased IgG4 was neither specific for IgG4-RD nor present in all individuals with histologically established IgG4-RD. Few patients with increased IgG4 levels have IgG4-RD, but a wide range of rheumatic, biliary, hepatic, or pancreatic disorders are also present (Ryu et al., 2012). Nevertheless, serum IgG4 measurements play an important role in the diagnosis and management of IgG4-RD, and there remains a possibility that IgG4 contributes to the pathophysiology of tissue injury in this disease either directly or indirectly. Patients with IgG4-RD can have elevations of all IgG subclasses, but the elevations of IgG4 are usually disproportionate to those of IgG1, -2, and -3. Patients with multiorgan disease can have dramatic elevations in serum IgG4 concentrations, occasionally exceeding 4 mg/dL. Despite the substantial elevations in

serum IgG4 concentrations observed in most patients with IgG4-RD, IgG4 itself is unlikely to drive the pathogenesis of this disorder. As per the recent interesting study serum IgG4 levels appear to be correlated with disease activity, suggesting more inflammatory IgG4-RD types. Higher inflammatory marker changes, extended involvement of organs and decreased levels of complement are common in individuals with high IgG4 levels (Inoue et al., 2015; Wallace et al., 2015; Stone et al., 2015). Serum IgG4 levels may also be affected by the location of IgG4-RD as these levels are increased in AIP patients and decreased in the majority of patients having IgG4-related RPF (Wallace et al., 2015), likely due to less IgG4+ plasma cells in dense fibrotic tissues in RPF (Deshpande et al., 2012). In addition, IgG4+ plasmablasts were enumerated in a group of patients where these made up 61% of the total number of plasmablasts and tend to be greater in individuals with elevated blood IgG4 levels (Wallace et al., 2015). Additionally, compared to whole plasmablast count, there was a strong association between IgG4-RI and IgG4+ plasmablast levels (Wallace et al., 2015).

The incidence of intense lymphoplasmacytic infiltrate richly loaded with IgG41 plasma cells is the hallmark physiologic findings of IgG4-related disease (Deshpande et al., 2012). This lymphoplasmacytic infiltrate is whorled by irregular fibrotic development referred to as "storiform" fibrosis. Obliterative phlebitis is observed in majority of the patients, which result in destruction of the venous lumen. Phlebitis without obliteration, nonnecrotizing arteritis and tissue eosinophilia are among the low characteristic features seen in IgG4-RD. Obliterative arteritis is likewise seen in several tissues, specially the lung. Eosinophilic infiltration takes place in around 50% of patients, in spite of the tissue implicated.

The most common IgG4-RD manifestation was traditionally thought to be pancreatitis (Inoue et al., 2015), while tissue distribution greatly vary between different studies and is also influenced by the medical and hospital specialties (Wallace et al., 2015). In a cohort Japanese study, 60% of the 235 cases with IgG4-RD had pancreatitis, followed by 34% who had sialadenitis, 23% who had tubulointerstitial nephritis, 23% who had dacryoadenitis, and 20% who had periaortitis. Pancreatitis was the most prevalent manifestation, but 58% of cases included several organs (Inoue et al., 2015). Furthermore, it cannot be ignored that the prevalence of IgG4-RD in European/American and Asian individuals varies not only generally but also in terms of the specific organ presentations (Wallace et al., 2015). Moreover, certain organ involvement patterns may be localized. According to reports, AIP is usually linked to IgG4-related cholangitis and kidney disorders, and sialadenitis frequently coexists with dacryoadenitis. On the other hand, it appears that IgG4-related kidney disorders rarely coexist with RPF (Wallace et al., 2015).

The lymphadenopathy linked with IgG4-related diseases is in general, either a local lymphadenopathy or comprehensive disorder adjacent to the diseased organ with non tender lymph nodes usually measuring 1−3 cm in diameter. Dacryoadenitis (enlargement of lacrimal glands) is the most regular ophthalmic manifestation in IgG4-RD. The triad

consisting of enlargement of lacrimal, submandibular and parotid glands once known as "Mikulicz' disorder," is currently known to be a characteristic feature in individuals with IgG4-related diseases. Allergic rhinitis, continual sinusitis, nasal polyps, rhinorrhea and nasal obstruction are common findings in IgG4-related diseases.

Imaging methods are often helpful for making differential diagnoses and determining the severity of the disease, but they do not present symptoms exclusive to IgG4-RD. A useful diagnostic tool for IgG4-RD, 18F-fluorodeoxyglucose positron emission tomography (FDG PET)/CT can be used to show up active inflammatory lesions, which enable to assess the disease severity. Moreover, FDG PET/CT is also a helpful technique for screening and staging disease activity, for assessing treatment response, and for directing biopsies (Ebbo et al., 2014; Nakatani et al., 2012; Vasaitis, 2015; Zhang et al., 2014). In a recent finding, over 70% of IgG4-RD patients had a greater extent of organ involvement than was previously contemplated (Zhang et al., 2014). However, it has limited utility, particularly for tiny lesions and in kidney or brain manifestations (Ebbo et al., 2014).

3. Conclusion

The Systemic autoimmune diseases engross a broad spectrum of related disorders which are best regarded jointly. These are caused by improper immune reactions that induce damage to the self organs affecting any part of the body. The pathological features associated with these conditions are therefore diverse and often hard to identify. The major complexity associated with these disorders relates to community health issues. The occurrence and frequency data of these disorders in different communities are sparsely known and need to be exactly evaluated. It is apparent that the autoimmune diseases frequently occur in industrialized regions and they seem to be rising in the developing regions as well. Although over the past decade, new technologies have considerably increased our understanding regarding these diseases however the exact pathophysiology remains to be elusive. High-throughput technological tools to investigate genetic polymorphisms, gene expression, epigenetic alterations, protein expression and modification, affliated with well characterized database patient collection, make it feasible to verify the expression levels of huge amount of proteins or genes in definite patient populations and cell sub-populations. This information may offer novel paradigms into the disease pathophysiology and new methods to phenotype individuals for autoimmune diseases.

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CHAPTER 5

Exploring medicinal plants as promising approaches for myasthenia Gravis and Multiple Sclerosis treatment: An emerging approach to new medicines

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1. Introduction

The immune system is an intricate system that defends the host body from foreign pathogens, stresses, ailments and personal attacks. It is classified into two types: innate and adaptive immunity. In innate immunity, dendritic cells (DCs), macrophages, mast cells, neutrophils, basophils, eosinophils, invariant natural killer cells (NK cells), NKT cells and γδT cells are involved, while in adaptive immunity, T cells and B cells are involved (Garg et al., 2010). The immune system plays a role in fighting types of infections and parasitosis, such as those caused by bacteria, fungi, viruses, helminths, protozoa (Ullrich, 2010; Vesely et al., 2011) and others, which are actually caused or aggravated by the immune response. These include hypersensitivity, autoimmunity, immunodeficiency, and cancer (Delves et al., 2006).

Autoimmunity, the immune response against self, raises the specter of "horror autotoxicus," a term coined by Paul Ehrlich at the turn of the twentieth century to define the feared consequences of this condition (Silverstein, 2009). An autoimmune disease is generally diagnosed by the presence of adaptive immune system-mediated disease caused by self-reactive antibodies, T cells, or both. $CD4^+$ T cells participate in the immune response (Astry et al., 2015). The disparity between Th1 and Th2 cells has traditionally been suggested to play the key roles; however more recently identified Th17 and Treg subsets have captured the central place in autoimmune response (Kannan et al., 2018). There are over 80 different kinds of

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autoimmune disorders. The most common among them are: Addison disease, Celiac disease—sprue (gluten-sensitive enteropathy), Dermatomyositis, Graves' disease, Hashimoto thyroiditis, Multiple sclerosis, Myasthenia gravis, Pernicious anemia, Reactive arthritis, Rheumatoid arthritis, Sjögren syndrome, Systemic lupus erythematosus, Type I diabetes.

Autoimmune diseases are a type of illness that can affect multiple organs and can be systemic or organ specific. The failure of the self-tolerance mechanism by lymphocytes is thought to be the primary driver of the progression of autoimmune diseases (Liu et al., 2011). Surprisingly, according to the American Autoimmune Related Disorders Association (AARDA), the prevalence of autoimmune illness is higher (75%) in women than in men. The global incidence and prevalence of autoimmune illnesses have grown dramatically, accounting for 19.1% and 12.5%, respectively (Rosenblum et al., 2015). The percentage rise each year for neurological, gastrointestinal, endocrinological, and rheumatic autoimmune illnesses is 3.7%, 6.2%, 6.3%, and 7.1%, respectively (Lerner et al., 2015).

Most immune-associated diseases are known to be correlated with inflammation. Inflammation is a critical immune response that underpins many processes, allows for survival and tissue repair, and maintains organ and body homeostasis. It is composed of four components: inducers, sensors, mediators, and target tissues (Medzhitov, 2008, 2010; Schmid-Schonbein, 2006). The types of inducers of inflammation are broadly classified into exogenous and endogenous (Medzhitov, 2008, 2010). Exogenous inducers are categorized into two subgroups: microbial (include pathogen-associated molecular patterns (PAMPs) and virulence factors) and nonmicrobial (include various allergens, irritants, foreign materials and toxic compounds (Medzhitov, 2008, 2010). However, endogenous inducers of inflammation are the signals produced by malfunctioning, stressed or damaged cells or tissues and can trigger distinct types of inflammatory responses, suggesting that they can play a vital role in immune response (Medzhitov, 2008). The number of endogenous pathways that initiate inflammatory responses are known to be dependent on reactive oxygen species (ROSs) activity. Therefore, ROS is considered a promising target for immunomodulation or antiinflammation (Jiang et al., 2007). Immune modulation is recognized as a critical technique for the treatment or management of a variety of immune-related disorders (Cho, 2008; Ouchi et al., 2011). Immunomodulation is a therapeutic technique that uses immunostimulators, immunosuppressants, and tolerogens to intervene or regulate immune responses to a desired level (Spelman et al., 2006).

Although the world is shifting from disease-treatment to disease-prevention health care, mainstream pharmaceutical research and development keeps concentrating on single molecules, biochemicals, or biologics as lead compounds. To address this, drug discovery and development methodologies based on systematic and modernized

examination of complementary and alternative medicine (CAM) or traditional medicine are reemerging as an appealing strategy. CAM practices include ancient and self-integrated medical systems such as Ayurvedic medicines and traditional Chinese medicine (TCM). Plant materials are the primary source of many of these medicinal compounds. Phytomedicines, including phytoextracts, their subfractions, or isolated single phytocompounds or phytochemicals are thought to interact with multiple targets to confer pharmacological or physiological effects at the cellular, tissue, or organ levels. They have been demonstrated to provide a range of immunomodulatory actions in experimental settings, suggesting that they are quite safe (Hou et al., 2010; Shyur & Yang, 2008).

Natural product-derived medications have been used for 5000 years (Goldman, 2001) with up to 80% of people worldwide relying on herbal remedies to treat immunological problems, as estimated by WHO (Licciardi & Underwood, 2011). Moreover, nearly 30% of all FDA-approved medications are derived from botanical origin (Licciardi & Underwood, 2011; Onaga, 2001). Therefore, medicinal plants could be a promising complementary or alternative approach for the treatment of various autoimmune diseases. Several studies have shown that various plants have beneficial effects in improving symptoms of Myasthenia gravis (MGs) and Multiple sclerosis (MSs) by reducing inflammation and oxidative stress. This chapter mainly focuses on the role of medicinal plants in treating Myasthenia gravis and Multiple sclerosis. However, further research is needed to explore the efficacy and safety of these plant-based therapies for the management of MG and MS.

2. Myasthenia gravis

Myasthenia gravis (MGs) is an acquired autoimmune condition characterized by a disruption in neuromuscular junction transmission mediated by autoantibodies directed mainly toward the acetylcholine receptor (AChR) and muscle-specific kinase (MuSK) (Sanders et al., 2016). Moreover, around 10%−15% of the double-negative MG patients have antibodies to lipoprotein-related protein 4 (LRP4) (Li et al., 2018). The Agrin-LRP4-MuSK protein complex is required for NMJ (neuromuscular junction) development and maintenance, including AChR distribution and clustering (Li et al., 2018). MG causes exhaustion and generalized weakness of the skeletal muscles, which can involve the respiratory muscles and lead to a myasthenic crisis. Muscle weakness results from impaired transmission of electrical impulses across the neuromuscular junction caused by the development of autoantibodies against certain postsynaptic membrane proteins. It is more prominent in the afternoon and usually involves muscles of the eyes, throat, and extremities. A variety of conditions can cause MG, such as infections, immunizations, surgeries, and drugs.

2.1 Epidemiology

Acquired myasthenia gravis (MGs) is a relatively unusual disorder, with prevalence rates that have surged to about 20 per 100,000 in the US population. The incidence rate of MG ranged from 0.3 to 3.0 per 100,000 worldwide (McGrogan et al., 2010; Zieda et al., 2018). Myasthenia gravis appears to be influenced by age and sex. It shows a feminine predominance in people under the age of 40 and a male predominance in people beyond the age of 50. The female to male ratio is approximately 3:1 in those under the age of 40; however, it is roughly equal between the ages of 40 and 50 as well as throughout puberty (Grob et al., 2008). Childhood MG in Asian countries, is frequent, affecting about 50% of children under the age of 15, but is relatively uncommon in western countries, accounting for 10%–15% of MG cases (Zhang et al., 2007). Extrinsic ocular muscle involvement (EOMs) is the primary symptom in around two-thirds of patients. It typically progresses to further bulbar muscles and limb musculature, resulting in generalized myasthenia gravis (gMGs) (Trouth et al., 2012; Zhang et al., 2007). In about 10% of MG patients, symptoms are restricted to EOMs, which results in a condition called ocular MG (oMG) (Conti-Fine et al., 2006).

2.2 Classification of myasthenia gravis

MG is divided into following six subtypes on the basis of the type of clinical characteristics and the type of antibodies involved: Each group has a different prognosis value because they respond differently to treatments (Gilhus et al., 2011).

1. Early-onset MG: period of commencement less than 50 years with thymic hyperplasia, often females.
2. Late-onset MG: period of commencement greater than 50 years with thymic atrophy, mostly in males.
3. Thymoma-associated MG (10%–15%).
4. MG with antiMuSK antibodies.
5. Ocular MG: symptoms only from periocular muscles.
6. MG with no detectable AChR and MuSK antibodies (muscle-specific tyrosine kinase antibodies).

AChR antibodies are generally present in the blood of MG patients with thymoma. In addition to that they may also have paraneoplasia-associated antibodies (e.g., antivoltage-gated K^+ and Ca^{++} channels, antiHu, antidihydropyrimidinase-related protein 5, and antiglutamic acid decarboxylase antibodies (Leite et al., 2010; Meriggioli & Sanders, 2009).

2.2.1 Clinical classification

Based on the clinical characteristics and nature of the disease, the Myasthenia Gravis Foundation of America (MGFA) clinical classification classifies MG into five main classes

and various subclasses. It is aimed at distinguishing subgroups of MG patients who have similar clinical characteristics or levels of disease severity and who may have differing prognoses or therapeutic outcomes (Jaretzki et al., 2000).

2.2.1.1 Class I MG is characterized by the following

(i) Any ocular muscle weakness.
(ii) May have weakness in eye closure.
(iii) All other muscle strengths are normal.

2.2.1.2 Class II MG is characterized by the following

(i) Mild weakness affecting muscles other than ocular muscles.
(ii) May also have ocular muscle weakness of any severity.

2.2.1.3 Class IIa MG is characterized by the following

(i) Predominantly affecting limb, axial muscles, or both.
(ii) May also have lesser involvement of oropharyngeal muscles.

2.2.1.4 Class IIb MG is characterized by the following

(i) Predominantly affecting oropharyngeal, respiratory muscles, or both.
(ii) May also have lesser or equal involvement of limb, axial muscles, or both.

2.2.1.5 Class III MG is characterized by the following

(i) Moderate weakness affecting muscles other than ocular muscles.
(ii) May also have ocular muscle weakness of any severity.

2.2.1.6 Class IIIa MG is characterized by the following

(i) Predominantly affecting limb, axial muscles, or both.
(ii) May also have lesser involvement of oropharyngeal muscles.

2.2.1.7 Class IIIb MG is characterized by the following

(i) Predominantly affecting oropharyngeal, respiratory muscles, or both.
(ii) May also have lesser or equal involvement of limb, axial muscles, or both.

2.2.1.8 Class IV MG is characterized by the following

(i) Severe weakness affecting muscles other than ocular muscles.
(ii) May also have ocular muscle weakness of any severity.

2.2.1.9 Class IVa MG is characterized by the following

(i) Predominantly affecting limb, axial muscles, or both.
(ii) May also have lesser involvement of oropharyngeal muscles.

2.2.1.10 Class IVb MG is characterized by the following

(i) Predominantly affecting oropharyngeal, respiratory muscles or both.
(ii) May also have lesser or equal involvement of limb, axial muscles, or both.

2.2.1.11 Class V MG is characterized by the following

(i) Intubation with or without mechanical ventilation, except when employed during routine postoperative management.
(ii) The use of feeding tube without intubation places the patient in class IVb.

2.3 Pathophysiological mechanism

Depending on the type of antibodies present, various pathophysiologic pathways appear in MG.

In n-AChR MG; IgG1 and IgG3 antibodies are present. They interact with the n-ACh receptor in the skeletal muscle postsynaptic membrane, activating the complement system and resulting in the membrane attack complex to develop (MAC). The receptors are eventually degraded as a result of MAC. They may also work by functionally preventing ACh binding to its receptor or by promoting the endocytosis of the antibody-bound n-ACh receptor (Suresh & Asuncion, 2022).

In MusK MG and LPR4 MG; IgG4 antibodies are present, which lack complement activation. They interact with the Agrin-LRP4-MuSK protein complex in the NMJ, which has the fundamental role of maintaining the NMJ, including the distribution and clustering of n-ACh receptors. The inhibition of the complex leads to a reduced number of n-ACh receptors (Conti-Fine, 2006; Verschuuren et al., 2013). Because of the significant reduction in the number of n-ACh receptors, the ACh produced at the nerve terminal is unable to create the postsynaptic potential necessary to trigger an action potential in muscle, resulting in muscular weakening symptoms. The weakness becomes more apparent when a muscle group is used frequently because it exhausts the Ach supply in the NMJ.

2.4 Histopathology

The type of antibodies present affects histopathological findings in MG:

Muscle: Muscle atrophies are prominent in n-AChR MG, whereas minor muscle atrophies and severe mitochondrial abnormalities are present in MuSK MG (giant, swollen, and degenerative features). The findings indicate that the two subtypes of MG have distinct pathophysiologic processes; neurogenic atrophy appears to be significant in n-AchR MG, whereas mitochondrial abnormalities are seen in MuSK MG (Cenacchi et al., 2011).

Thymus: Epithelial hyperplasia and extraparenchymal involvement with T-cell regions and germinal centers (GCs) are seen in n-AChR MG while in MuSK MG the

thymus changes with age and hyperplastic alterations are quite rare. Infiltrates are observed in 50% of individuals with seronegative MG (Leite et al., 2007). These observations of thymic epithelial hyperplasia and T-cell infiltration suggest that the thymus is involved in the generation of autoantibodies against muscle proteins.

2.5 Symptoms of MG

Myasthenia gravis produces a wide range of symptoms. The following are the most prevalent symptoms:

Extraocular Muscle Weakness: This is seen in around 85% of patients at the onset. Diplopia, ptosis, or both are common patient complaints. During the next two years, 50% of patients would develop generalized MG including the bulbar, axial, and limb muscles (Grob et al., 1987).

Bulbar Muscle Weakness: This is the first presentation in 15% of patients and involves symptoms such as difficulty chewing or frequent choking, dysphagia, hoarseness, and dysarthria (Grob, 1953; Grob et al., 1987; Pal & Sanyal, 2011). Facial muscle involvement results in an expressionless face, whereas neck muscle involvement results in dropped-head syndrome.

Limb Weakness: This often affects the proximal muscles more than the distal muscles, with the upper limbs being more impacted than the lower limbs (Werner et al., 2003).

Myasthenic crisis: This Can occur as a result of respiratory muscle dysfunction. It is characterized by the involvement of the intercostal muscles and diaphragm and is a medical emergency that requires artificial breathing and naso-gastric (NG) tube feeding (Murthy, 2020). It can be caused by infections and drugs such as aminoglycosides, telithromycin, neuromuscular blocking agents, magnesium sulfate, beta blockers, and fluoroquinolone antibiotics (Keesey, 2004).

Because MG solely affects the nicotinic cholinergic receptors, no autonomic symptoms like palpitations, bowel or bladder problems, or sweating occur.

2.6 Complications

Myasthenic crisis is a complication of myasthenia gravis that is mainly caused by infections, stress, or severe diseases (Suresh & Asuncion, 2022). Long-term steroid effects include osteoporosis, hyperglycemia, cataracts, weight gain, hypertension, and hip avascular necrosis. With continuous immunosuppressive medication, there is also a risk of lymphoproliferative malignancies and opportunistic infections such as systemic fungal infections, TB, and Pneumocystis carinii pneumonia. Cholinergic crisis occurs as a result of excessive ACh at nicotinic and muscarinic receptors caused by cholinesterase inhibitor use. Some of the symptoms are Cramping, lacrimation, increased salivation, muscular weakness, muscular fasciculation, paralysis, diarrhea, and blurred vision.

2.7 Diagnosis of MG

Most MG diagnoses are done clinically. Normally, the laboratory tests and procedures help the clinician confirm the clinical findings.

Tensilon (Edrophonium Chloride) Test: Edrophonium is a short-acting acetylcholinesterase inhibitor that intensifies acetylcholine's activity at the NMJ. It is given intravenously in Ocular MG and is monitored for progress in symptoms of ptosis or diplopia. Side effects include increased salivation, sweating, nausea, stomach cramping, and muscle fasciculation. Tensilon test has a sensitivity of 71.5%–95% (Meriggioli & Sanders, 2005; Pascuzzi, 2003; Trouth et al., 2012).

Ice-pack Test: When edrophonium testing is not appropriate, an ice-pack test is an alternative. This procedure necessitates the application of an ice compress to the eye for 2–5 min. Then, any change in ptosis is evaluated. This test cannot be used to evaluate extraocular muscles.

Serologic Tests: The antiAChR Ab-test is highly sensitive to MG, detecting it in four-fifths of patients with generalized MG and only half of those with pure ocular MG (Lindstrom et al., 1976). This test has a sensitivity of about 85% for gMG and 50% for oMG (Lennon, 1997; Vincent & Newsom-Davis, 1985). The remaining patients, about 5%–10%, will have antiMuSK antibodies. Only in a few odd cases have antiAChR and antiMuSK antibodies been found in the same patient. AntiLRP4 antibodies will be detected in 3%–50% of the remaining individuals who are seronegative to any of these antibodies. 30% of MG patients have antistriated muscle antibodies. They are more helpful as a thymoma serologic marker, especially in younger individuals (Statland & Ciafaloni, 2013; Leite et al., 2007; Juel et al., 2007).

Electrophysiologic Tests: For MG there are the Repetitive Nerve Stimulation (RNS) test and Single Fiber Electromyography (SFEMG). Repetitive nerve stimulation tests neuromuscular transmission by stimulating the nerve supramaximally at 2–3 Hz. A 10% decrement between the first and fifth evoked muscle action potentials is diagnostic for MG. Exercise can be used to induce exhaustion of muscles and document decrement (Oh et al., 1992; Sanders et al., 1979). The most reliable diagnostic tool for MG is single fiber electromyography (SFEMG), which facilitates the simultaneous monitoring of action potentials produced by two muscle fibers innervated by the same motor axon. Jitter, the variability of the second action potential relative to the first, rises in MG owing to a decreased transmission safety factor at the neuromuscular junction. 95%–99% of individuals have aberrant jitter in SFEMG (Oh et al., 1992; Sanders et al., 1979).

Imaging: Chest computed tomography (CT) or magnetic resonance imaging (MRI) should be performed in patients with MG to assess for thymoma and ocular MG to evaluate for localized mass lesions. Iodinated contrast agents should be used with caution to prevent myasthenic weakness (Chagnac et al., 1985; Eliashiv et al., 1990).

Other Laboratory Tests: Because myasthenia gravis is frequently associated with other autoimmune diseases, checking for antinuclear (ANA) antibodies, rheumatoid factor (RF), and basal thyroid functions is advised (Trouth et al., 2012).

2.8 Treatment/management

To treat MG, four basic therapies are employed (Trouth et al., 2012).

2.8.1 Symptomatic treatment with acetylcholinesterase inhibitors

Acetylcholinesterase inhibitors are the first-line treatment and work by enhancing the levels of available acetylcholine at the NMJ (Drachman, 1994). Pyridostigmine represents the most widely used drug, with an immediate onset of action and peak activity in 2 hours. The initial recommended oral dosage is 15–30 mg every 4–6 h which is gradually increased depending on the patient's response. Adverse side effects are caused mainly by the cholinergic characteristics of drug and include abdominal cramping, diarrhea, increased salivation and bronchial secretions, nausea, sweating, and bradycardia. Nicotinic side effects include muscle fasciculation and cramping (Bosch et al., 1991). Bromide intolerant patients are administered ambenonium chloride. Individuals with MuSK MG have a poor response to these medications and may require greater dosages (Melzer et al., 2016).

2.8.2 Rapid short-term immunomodulating treatment with plasmapheresis and intravenous immunoglobulins

Plasmapheresis: It increases strength in MG patients by eliminating AChR from the bloodstream (Batocchi et al., 2000). Normally, one exchange is performed every other day, for a total of four to six times. Adverse effects include hypotension, paresthesias, infections, thrombotic problems and bleeding (Gold & Schneider-Gold, 2008).

Intravenous Immunoglobulin Therapy (IVIg): Immunoglobulins recovered from pooled human plasma by ethanol cryoprecipitation are extracted and delivered at a dosage of 0.4 g/kg/day for 5 days. The mode of action for IVIg's is complicated, including inhibition of cytokine competition with autoantibodies, inhibition of complement deposition, interference with Fc receptor binding on macrophages, Ig receptor binding on B cells, and interference with antigen detection by sensitized T cells (Samuelsson et al., 2001). In clinical studies, individuals treated with immunoadsorption approaches had significant reductions in blocking antibodies along with clinical improvement (Psaridi-Linardakiet al., 2005). While, IVIg is thought to be safe, problems do arise in rare circumstances (Brannagan et al., 1996).

IVIg and plasma exchange (PLEX) have similar effectiveness, mortality, and complications (Barth et al., 2011); however, PLEX has a cost benefit ratio of 2: 1 for the management of MG (Robinson et al., 2012).

2.8.3 Chronic long-term immunomodulating treatment with corticosteroids and other immunosuppressive drugs

The objective of immune directed treatment for MG is to produce and sustain remission or near-remission of symptoms (Trouth et al., 2012). Immunosuppressive therapy is recommended for people who are still symptomatic following pyridostigmine treatment.

Immunosuppressive Treatment: The first-line immunosuppressive therapies used in the treatment of MG include corticosteroids, for example Glucocorticoids (prednisone, prednisolone, and methylprednisolone). Prednisone is often used when cholinesterase inhibitors alone are insufficient to treat symptoms. Transient exacerbation can occur after initiating massive doses of prednisone within the first 7–10 days (Evoli et al., 1992; Pascuzzi et al., 1984). Cholinesterase inhibitors are frequently employed to treat this deterioration. Plasma exchange or IVIg can be administered before prednisone therapy to avoid or minimize the degree of corticosteroid-induced weakness and to produce a quicker response. In oMG, oral prednisone could prove more effective than anticholinesterase medications (Bhanushali et al., 2008; Kupersmith et al., 1996).

Nonsteroidal Immunosuppressive Agents: Azathioprine, a purine derivative, inhibits T- and B-cell proliferation by suppressing nucleic acid synthesis. It is the most frequently used immunosuppressive agent in MG, and is efficacious in 70%–90% of patients, with clinical response taking up to 15 months to detect. It is more effective and well tolerated when administered with prednisone than prednisone alone (Palace et al., 1998). Hepatotoxicity and leukopenia are two of the undesirable side effects (Kissel et al., 1986). Cyclosporine, mycophenolate, cyclophosphamide, tacrolimus and methotrexate are the second-line agents that are used when the patient is unresponsive, has potential complications, or is intolerant to first-line treatment.

CyclosporineA (CyA) is a steroid-sparing drug that is used to inhibit the formation of IL-2 cytokine receptors and other proteins required for the function of $CD4^+$ T cells. It is used in individuals who do not react to azathioprine (Tindall et al., 1993).

Mycophenolate mofetil (MMF) specifically inhibits purine synthesis, affecting both T-cell and B-cell proliferation. It is administered at 1000 mg twice daily; however, dosages of up to 3000 mg daily are acceptable (Chaudhry et al., 2001; Ciafaloni et al., 2001). Higher doses are linked with myelosuppression; it is not recommended during pregnancy and should be taken with caution in individuals with renal illness, GI disease, bone marrow suppression, or elderly people (Meriggioli et al., 2003).

Cyclophosphamide administered intravenously and orally is an effective treatment for MG (Spring & Spies, 2001), but has side effects such as hair loss, nausea, vomiting, anorexia, and skin discoloration (Conti-Fine, 2006). It can be used in combination with bone marrow transplant or rituximab/eculizumab, a monoclonal antibody against the B cell surface marker CD20 to treat resistant patients (Pescovitz, 2006; Melzer et al., 2016).

Tacrolimus has the potential benefit of being less nephrotoxic than cyclosporine, but it can have serious negative consequences (Conti-Fine, 2006).

Etanercept, a soluble and recombinant tumor necrosis factor-α (TNF-α) receptor blocker, has also been reported in small-group trials to have steroid-sparing properties (Conti-Fine, 2006; Tuz et al., 2005).

Methotrexate, there has been no research on the use of methotrexate in MG. However, after all other treatment options have been exhausted; the medication might be explored in treatment-resistant individuals. Long-term toxicity should always be considered.

2.8.4 Surgical treatment

Due to the heterogeneity of MG, there is no globally recognized standard of care, and no single treatment is optimal for all patients (Sanders et al., 2016, 2018).

Thymectomy: Surgical treatment is suggested for individuals with thymoma, but it may not be a feasible therapeutic option for patients with antiMuSK antibody positive patients due to the absence of germinal centers in thyme and lymphocyte infiltrates that characterize thyme in patients with antiAChR antibodies (Gronseth & Barohn, 2000; Lavrnicet al., 2005).

2.9 Rehabilitation

In addition to other types of medical treatment, a rehabilitation program can help alleviate symptoms and enhance performance for people with MG. It is suggested to use a multidisciplinary strategy that includes neuromuscular medicine, physical medicine and rehabilitation, and respiratory therapy. Physical therapy has advantages for long-term muscle strength restoration, graded strengthening exercises help the individual remain functional, occupational therapy helps the individual adapt to new ways of performing daily living tasks, speech therapy trains esophageal speech after a tracheostomy, and vocational counseling may be required. Psychological treatments may be required as well (Trouth et al., 2012).

3. Role of medicinal plants in treating MG

Traditional Chinese medicine (TCM), among the world's comprehensive medical systems, has a thousand-year history and is currently widely practiced in China as well as globally. In present times, Chinese herbal medicine (CHM), one of TCM's key therapeutic interventions, is frequently utilized in treatment for MG and has received experimental proof (Cui et al., 2015; Orhan, 2013). However, because of the low methodological quality of the main studies, the existing data is insufficient to recommend CHM as a standard treatment for MG (Lyu & Sun, 2015). The most frequently used

herbs and the pharmacological effects of their active compounds used for the treatment of MG are listed here (Chen et al., 2018).

1. *Radix Astragali seu Hedysari/Astragalus membranaceus (milk vetch root):* promoting the expression of transcription factor Forkhead box protein P3 (FoxP3) to up-regulate T regulatory cells (Tregs) (Jin et al., 2013; Qu et al., 2010) and decreasing cytokine expression such as IL4 and IL-13 (Chen, Tsai, et al., 2014; Zhao et al., 2016).
2. *Radix Bupleuri (Chinese thorowax root)-Bupleurum polysaccharides (BPs) from Radix Bupleuri:* a decrease of autoantibodies and immunoglobulin G (IgG) (Wang et al., 2009).
3. *Ra*dix Ginseng (ginseng)-increasing the number of Tregs and inhibiting Th17 cell differentiation (Bae et al., 2012; Chen, Wu, et al., 2014; Chen et al., 2016; Jhun et al., 2014; Lee et al., 2015).
4. *Huperzine A (HupA)*, isolated from *Huperzia serrata* and flavonoid derivatives from Buzhongyiqi Decoction exhibited antiacetylcholinesterase effects (Cui et al., 2015; Orhan, 2013).

In addition to this, a large number of plants that have been used to prepare herbal formulations which that been proven to improve the symptoms of Myasthenia gravis are listed here.

1. Jian Ji Ning (JJN), a traditional Chinese medicine formula consisting of 11 medicinal plants, that has been used in the treatment of MG for many years, such as *Radix Astragali seu Hedysari*, *Radix Pseudostellariae*, *Rhizoma Atractylodis Macrocephalae*, *Fructus Aurantii*, *Rhizoma Cimicifugae*, *Herba Leonuri*, *Radix Saposhnikoviae*, *Radix Angelicae Sinensis*, *Fructus Lycii*, *Radix Polygoni Multiflori*, and *Fructus Corni*. JJN has a curative effect on patients with MG-induced neuropathologic changes due to its inhibition of apoptotic pathways and regulation of serum miRNAs (Jiang et al., 2014).
2. Huangqi Fufang granule (HQFF), a traditional Chinese medicine formula consisting of following medicinal plants; *Radix Astragali seu Hedysari* 50 g, *Radix Pseudostellariae* 25 g, *Rhizoma Atractylodis Macrocephalae* 15 g, *Rhizoma Cimicifugae* 10 g, *Radix Saposhnikoviae*10 g, *Radix Angelicae Sinensis* 10 g, *Fructus Lycii* 15 g, *Fructus Corni* 15 g. It has been reported to reduce symptoms of myasthenia gravis (MG), and restore the balance of gut microbial community, or microbiota, in people with mild MG. Adjusting the balance of the gut microbiota could be an important approach for treating MG (Niu, 2009).
3. Qiangji Jianli Yin (QJJLY) is a herbal formulation prepared from *Radix Astragali seu Hedysari*, *Radix Codonopsis*, *Rhizoma Atractylodis Macrocephalae*, *Radix Angelicae Sinensis*, *Rhizoma Cimicifugae*, *Radix Bupleuri*, *Pericarpium Citri*, *Radix Glycyrrhizae*, *Cayratia japonica*. The curative effect of routine treatment with added Qiangjijianli yin is much better than that of only immunosuppressants' method. This new method has the function of regulating the secretion of inflammatory cytokines, thus reducing complications (Ou, 2005).

4. Tan Wei Capsule (TW) is a traditional Chinese medicine formulation that contains four main ingredients: *Radix Astragali seu Hedysari*, *Placenta Hominis*, *Semen Strychni*, and *Radix Glycyrrhizae*. It has been reported to have immunomodulatory and anti-inflammatory properties (Ju, 2003).
5. Yiqi Chushi Recipe (YQCS), a herbal formulation prepared from *Radix Astragali seu Hedysari* 30 g, *Rhizoma Atractylodis*15 g, *Semen Coicis* 30 g, *Radix Achyranthis Bidentatae* 10 g, *Semen Arecae* 10 g, *Fructus Chaenomelis* 15 g, *Radix Angelicae* 15 g, *Radix Salviae Miltiorrhizae* 15 g, *Poria* 15 g, *Radix Bupleuri* 10 g, *Radix Glycyrrhizae* 10 g. It has been reported that the treatment had a significant effect on improving muscle strength and reducing symptoms of fatigue. Therefore, it may be a safe and effective treatment for myasthenia gravis (Shuang & Tan, 2014).
6. Buzhong Yiqi decoction (BZYQ), a herbal formulation prepared from; *Pericarpium Citri* 15 g, *Radix Angelicae Sinensis* 10 g, *Radix Codonopsis* 30 g, *Radix Glycyrrhizae* 5 g, *Rhizoma Cimicifugae* 10 g, *Rhizoma Atractylodis* 15 g, *Radix Astragali seu Hedysari* 60 g, *Radix Bupleuri* 10 g. Buzhong Yiqi decoction (BZYQ) in combination with hormone therapy, showed significant effects on improving muscle strength, reducing symptoms of fatigue, and increasing the levels of acetylcholine receptor antibodies (AchR-Ab) in the patients. Therefore, it suggests that it may have a beneficial effect on myasthenia gravis, possibly through its immune-modulating and neuroprotective properties (Zu, 2015).
7. Bupi Qiangli Compound (BPQL) is a traditional Chinese herbal formulation prepared from; *Radix Astragali seu Hedysari* 60 g, *Radix Codonopsis* 20 g, *Rhizoma Atractylodis Macrocephalae* 15 g, *Radix Angelicae Sinensis* 12 g, *Herba Epimedii* 15 g, *Radix Aconiti Lateralis Preparata* 40 g, *Rhizoma Smilacis Glabrae* 20 g. This herbal formula aims to tonify the Qi and nourish the blood. It has been shown to have significant improvements in muscle strength, a reduction in fatigue, and increased levels of immune markers, including T lymphocyte subsets and cytokines. Therefore, it could have a beneficial effect on myasthenia gravis by modulating the immune system and improving the Qi and blood circulation (Lai, 2013).
8. Ji Li Kang Drinking (JLK), is a traditional Chinese herbal formulation prepared from; *Radix Astragali seu Hedysari*, *Radix Codonopsis*, *Rhizoma Atractylodis Macrocephalae*, *Semen Coicis*, *Radix Angelicae Sinensis*, *Rhizoma Cimicifugae*, *Radix Bupleuri*, *Cayratia japonica*, *Radix Polygoni Multiflori Preparata*. This herbal formula has been used for the treatment of spleen deficient type myasthenia gravis, and it showed significant improvement in muscle strength, a reduction in fatigue, and increased levels of immune markers, including T lymphocyte subsets and cytokines. Therefore, it could have a beneficial effect on myasthenia gravis by improving the function of the spleen and nourishing the Qi and blood (Liang, 2011).
9. YiqiQushi Fang (YQQSF), a traditional Chinese herbal formulation prepared from; *Radix Astragali seu Hedysari* 60 g, *Radix Ginseng* 15 g, *Rhizoma Atractylodis*

*Macrocephalae*15 g, *Radix Angelicae Sinensis* 15 g, *Rhizoma Atractylodis* 12 g, *Rhizoma Alismatis* 12 g, *Rhizoma Cimicifugae* 9 g, *Cortex Phellodendri* 9 g. It showed a significant improvement in muscle strength, a reduction in fatigue, and increased levels of immune markers, including T lymphocyte subsets and cytokines. Therefore, it could have a beneficial effect on myasthenia gravis by regulating the immune system, improving the function of the spleen and kidney, and eliminating dampness and phlegm (Li, 2012).

10. Fuyuan Yiji Capsule (FYYJ), is a traditional Chinese herbal formulation prepared from; *Radix Ginseng*, *Cornu Cervi Pantotrichum*, *Rhizoma Atractylodis Macrocephalae*, *Poria*, *Radix Rehmanniae Preparata*, *Radix Bupleuri*, *Rhizoma Ligustici Chuanxiong*, *Rhizoma Acori Tatarinowii*, *Radix Gentianae*, *Radix Glycyrrhizae*. Fuyuan Yiji Capsule is used in combination with pyridostigmine bromide for the treatment of myasthenia gravis. It showed a significant improvement in muscle strength, a reduction in fatigue, and decreased frequency and severity of myasthenic crizes. Therefore, it may have a synergistic effect on myasthenia gravis by improving the function of the immune system, tonifying the Qi and nourishing the blood, and enhancing the efficacy of conventional drugs (Wang et al., 2008).
11. Zhongjiling Tablet (ZJL), is a traditional Chinese herbal formulation prepared from; *Cornu Cervi Pantotrichum*, *Radix Ginseng*, *Semen Cuscutae*, *Radix Astragali seu Hedysari*, *Fructus Lycii*, *Radix Angelicae Sinensis*, *Herba Ephedrae*, *Herba Epimedii*, *Placenta Hominis*, *Rhizoma Atractylodis*, *Poria*. This herbal formula aims to tonify the Qi, nourish the blood, and regulate the immune system. It showed a significant improvement in muscle strength, reduction in fatigue, and decreased frequency and severity of myasthenic crizes. In addition to this, it may regulate the immune system by increasing the number and function of T lymphocyte subsets, regulating the balance of Th1/Th2 cytokines, and reducing the level of autoantibodies. Therefore, it could have a beneficial effect on myasthenia gravis by regulating the immune system, tonifying the Qi and nourishing the blood, and improving the function of the spleen and kidney (Xu, 2006).
12. Zhongjiling Tablet (ZJL), is a traditional Chinese herbal formulation prepared from; *Cornu Cervi Pantotrichum*, *Radix Ginseng*, *Semen Cuscutae*, *Radix Astragali seu Hedysari*, *Fructus Lycii*, *Radix Angelicae Sinensis*, *Herba Ephedrae*, *Herba Epimedii*, *Placenta Hominis*, *Rhizoma Atractylodis*, *Poria*. This herbal formula aims to nourish the liver and kidneys, regulate the Qi and blood, and strengthen the spleen. Zhongjiling tablets in combination with conventional Western medicine showed significant improvements in the MGC (Myasthenia Gravis Composite) score, lower frequency of myasthenic crizes, and no significant difference in the levels of AChR-Ab. Therefore, Zhong Ji Ling tablets may be a safe and effective adjuvant therapy for myasthenia gravis when used in combination with conventional Western medicine (Xu et al., 2004).

13. Huangqi Fufang granule (HQFF), is a traditional Chinese herbal formulation prepared from; *Radix Astragali seu Hedysari*, *Rhizoma Cimicifugae*, *Radix Saposhnikoviae*, *Rhizoma Atractylodis Macrocephalae*, *Radix Bupleuri*, *Radix Angelicae Sinensis*, and *Fructus Lycii*. It has been used in combination with conventional Western medicine to evaluate the effectiveness of Huangqi compound granules in treating myasthenia gravis. It showed that the treatment group had a significantly greater improvement in the MGC (Myasthenia Gravis Composite) score and a lower frequency of myasthenic crizes compared to the control group. Therefore, it could be concluded that Huangqi compound granules may be a safe and effective adjuvant therapy for myasthenia gravis when used in combination with conventional Western medicine (Bao, 2016).

4. Multiple sclerosis

Multiple sclerosis (MSs) is a chronic inflammatory and demyelinating disease of the central nervous system (CNS) that causes inflammation, multifocal demyelination, axonal loss, and gliosis in both white and gray matter (Mansilla et al., 2021). Regulatory T cells (Tregs) are $CD4^{+}CD25+FoxP3+$ T-cells that play an important role in maintaining immunological tolerance and suppressing the damaging self-reactive T cells observed in MS (Goverman, 2009; Reddyet al., 2005). Their dysregulation and reduction in number may be responsible to for causing MS (Corsini et al., 2011; Sakaguchi et al., 2006). The secretion of cytokines like interleukin (IL)-17 and transforming growth factor-β 1 as well as particular transcription factors like retinoic acid-related orphan receptor (ROR) γ t and forkhead box P3 (FoxP3) regulate the interactions between Th17 and Tregs (Wraith et al., 2004; Park et al., 2005; Yang et al., 2008).

4.1 Epidemiology

It is one of the most frequent nontraumatic causes of illness, increasing globally (Browne et al., 2014) and affecting 2.5 million people worldwide (Mansilla et al., 2021; Pugliatti et al., 2002; Wollberg et al., 2014). MS is a chronic neurological condition that mainly affects young to middle-aged adults, with an incidence of 50−200 cases per 100,000 people (Farzaei et al., 2017). It more often affects women than men with a 3:1 (F: M) ratio (Orton et al., 2006), with symptoms improving in late pregnancy coinciding with high levels of estriol (Papenfuss et al., 2011). Since testosterone levels fall with age, men are more likely to acquire primary-progressive MS later in life (Kurth et al., 2014).

Smoking raises the risk of MS by 50% (Palacios et al., 2011); and the fact that organic solvents and smoked tobacco are correlated to the disease but not oral tobacco or snuff has led to the hypothesis that these agents produce posttranslational changes in the lungs through antigen presentation (Napier et al., 2016; Handel et al., 2011; Hedström et al., 2009). The primary genetic risk factor for MS is HLA-DRB1*1501 and other loci with

insignificant linkage disequilibrium with this allele (Hollenbach & Oksenberg, 2015; Jelcic et al., 2018; Patsopoulos et al., 2019). More than 150 SNPs (single nucleotide polymorphisms) have been associated to MS susceptibility in genome-wide association studies (Beecham et al., 2013). Mendelian randomization investigations show that vitamin D and obesity are independent risk factors for this illness (Manousaki et al., 2017; Rhead et al., 2016; Mokry et al., 2015, 2016).

MS prevalence rises with latitude but falls in Norway and the United States (Koch–Henriksen et al., 2010). The latitudinal gradient in MS prevalence is strongly correlated with UVB exposure, which boosts cutaneous vitamin D (vD) synthesis, which has been related to low vD levels, decreased vD consumption, decreased outdoor activity, and enhanced MS susceptibility due to genetic polymorphisms (Sintzel et al., 2017).

Migration studies reveal that MS is secondary to environmental exposure. It is a medium-to high-risk disease in the Middle East and North Africa (Heydarpour et al., 2015). Adult migrants from low-risk areas face minimal threats; however, children born to migrants in Europe face significant risk (Kurtzke et al., 2013).

4.2 Classifications and diagnostic criteria

MS is a complicated illness with a wide range of clinical and radiological manifestations. It was initially classified into four different phenotypes: relapsing-remitting MS (RRMSs), secondary-progressive MS (SPMSs), primary-progressive MS (PPMSs), and relapsing-progressive MS (RPMSs) (Lublin & Reingold, 1996). The updated multiple sclerosis classification scheme now includes the two additional categories of CIS (clinically isolated disease (CIS) and RIS (radiologically isolated syndrome (RIS) (Sand, 2015). The McDonald 2010 diagnostic criteria offer clear guidelines for the diagnosis of each type of multiple sclerosis.

Relapsing-remitting MS (RRMSs); (85%), characterized by acute relapses (acute or subacute incidents of new or growing neurologic impairment in the absence of fever or infection) followed by remission with complete or partial recovery.

Secondary-progressive MS (SPMSs); is described as gradual clinical deterioration over time following an initial relapsing phase, with or without acute exacerbations during the progressive course.

Primary-progressive MS (PPMSs); which accounts for 15% of all MS cases, is distinguished by clinical progression without relapse from disease inception.

Relapsing-progressive MS (RPMSs); term RPMS refers to the gradual accumulation of illness from the time of commencement, with periodic relapses. This subtype is hardly diagnosed since its characteristics overlap with those of other phenotypes (Mansilla et al., 2021).

Clinically isolated syndrome (CIS) is the initial presentation of a patient with clinical signs suggestive of a demyelinating activity. A patient is diagnosed when there is clinical

evidence of a single exacerbation and the MRI does not fully satisfy the RRMS criteria. Individuals with CIS have a high risk of achieving RRMS criteria in the future (Tintore et al., 2006; O'Riordan et al., 1998; Kuhle et al., 2015); early therapy is useful in avoiding subsequent relapses (Jacobs et al., 2000; Miller et al., 2014).

The term "radiologically isolated syndrome" (RIS) was coined in 2009 (Okuda et al., 2009) and the current official diagnostic criteria for RIS are based on that initial 2009 publication (Sand, 2015). RIS is a disorder in which abnormalities indicative of multiple sclerosis are seen in people who have never had clinical signs of the illness.

4.3 Pathogenesis

Multiple sclerosis (MSs) has no recognized etiology (Chaudhuri, 2013). However, myelin-specific T lymphocytes are thought to play an important role in its etiology (Bielekova et al., 2004). A complex combination of several genetic and environmental variables has been proposed to contribute to the disruption of peripheral immunological homeostasis and the activation of autoreactive T cells (Olsson et al., 2016). Characteristics like the presence of malfunctioning regulatory T cells (Tregs) 11 or dendritic cells (DCs) 12, as well as changes in cytokine production, may encourage the entrance of proinflammatory myelin-specific autoreactive T cells into the CNS (Dendrou et al., 2015; Langelaar et al., 2020). In this situation, IFN-γ-producing Th17.1 (CCR6+CXCR3+CCR4−) cells, memory B cell precursors, and IFN-γ-producing $CD8^+$ T cells are important for disrupting the permeability of the BBB in MS (Rahman et al., 2018). Aside from chemokine receptors and proinflammatory cytokines, adhesion molecules such as integrin α4β1 (VLA-4), which induces firm adhesion to vascular cell adhesion protein 1 (VCAM1) on brain endothelial cells, and activated leukocyte cell adhesion molecule promote the transmigration of pathogenic B and T cell subsets (Cayrol et al., 2008; Michel et al., 2019). MS can be triggered by CNS-intrinsic processes such as viral infection or neurodegeneration, with autoreactive lymphocyte infiltration arising as a subsequent phenomenon (Louveau et al., 2015; Ransohoff & Engelhardt, 2012).

Several environmental factors, including infectious agents (primarily viruses-Epstein—Barr virus), tobacco, diet (long-chain fatty acids, salt), gut microbiota, stress, sex hormones, puberty, vitamin D deficiency, obesity and smoking have been associated with disease initiation and progression (Efendi et al., 2015; Olsson et al., 2016).

Perivenular inflammatory lesions resulting in demyelinating plaques are a pathophysiological hallmark of MS (Karussis et al., 2014; Castro-Borrero et al., 2012; Hafler & Weiner, 1987). T-lymphocytes, dominated by MHC Class I restricted $CD8^+$ T-cells, are present in the inflammatory infiltrates; B-cells and plasma cells are also present, but in considerably lower numbers (Lassmann et al., 2013). Inflammation causes oligodendrocyte destruction and demyelination. In the early stages of the disease, axons are

generally intact; nevertheless, as the disease persists, permanent axonal damage develops (Prineas et al., 2001).

4.4 Symptoms/clinical features

Symptoms of MS emerge as a result of a disruption in CNS function mediated by an autoimmune demyelinating process.

4.4.1 Spinal cord syndrome

The most prevalent clinical manifestation of multiple sclerosis is linked with the abrupt onset of a partial transverse myelitis, mainly sensory issues consistent with the inclusion of the dorsolateral cord (Cree, 2014). Acute full transverse myelitis with paraplegia is exceptional and should trigger evaluation of additional illnesses such as neuromyelitis optica spectrum disorder (NMOSD) (Bourre et al., 2012). Motor symptoms, such as weakness, stiffness, and gait problems, prevail over sensory symptoms in PPMS. Due to the specific significance CSF plays in the diagnostic criteria for PPMS, lumbar puncture is suggested in instances of progressing myelopathy in which multiple sclerosis is suspected (Cree, 2014; Miller & Leary, 2007; Weisfeld-Adams et al., 2015).

4.4.2 Optic neuritis

Optic neuritis usually appears with an acute, unilateral, painful decline in visual acuity that peaks within a few days and starts to improve within a few weeks. Pain with eye movements is usually prevalent and low to moderate in intensity (The clinical profile of optic neuritis, 1991). Examination usually shows impairments in acuity, low contrast vision, and color perception deficits, as well as an afferent pupillary impairment (Bermel & Balcer, 2013). A funduscopic inspection is usually normal, but optic disc enlargement can be seen (Hickman et al., 2002).

4.4.3 Brainstem or cerebellar syndrome

Diplopia caused by internuclear ophthalmoplegia is the most prevalent brainstem manifestation of multiple sclerosis. Facial weakness or a lack of sensation may develop with abnormal eye movement or independently. Vertigo can result from a lesion anywhere along the sensory networks, and ataxia can result from a cerebellar lesion (Miller et al., 2012). Approximately 15% of PPMS patients will develop a progressive cerebellar or brainstem condition, which is characterized by progressively deteriorating ataxia and dysarthria, dysphagia, and diplopia (Miller & Leary, 2007).

4.4.4 Cognitive impairment

It is widespread in all multiple sclerosis phenotypes and appears in the early stages of the disease; however, it is significantly more apparent in progressive than relapsing multiple sclerosis (Sand, 2015).

4.4.5 Cerebral hemisphere lesions

Tumefactive brain lesions can cause a hemispheric syndrome characterized by aphasia, encephalopathy, and elevated intracranial pressure. Paroxysmal symptoms are brief, periodic, stereotyped symptoms such as a vibrating or shock-like feeling with neck flexion, tonic spasms, trigeminal neuralgia, or paroxysmal dysarthria (Rae-Grant, 2013; I.K. Sand, 2015).

4.4.6 Muscle spasity

Muscle spasticity is a typical consequence in 60% of MS patients, which produces movement problems, painful spasms, and sleep disturbances (Vukusicet al., 2007). These complications can cause serious conditions such as joint ankylosis, fibrous contractures, and pressure sores. It can also lead to functional impairment and necessitate nursing care (Beard et al., 2003).

4.4.7 Fatigue

Approximately 75%–95% of MS patients suffer from fatigue, and the majority of them report fatigue as their most severe MS-associated complication (Kim et al., 2011).

4.4.8 Other clinical presentations

Several clinical symptoms related to long-term medication include depression, anxiety, cardiotoxicity, infection, nausea, and anemia (Knippenberg et al., 2014).

4.5 Diagnosis

The most recent diagnostic criteria for multiple sclerosis are the 2010 McDonald criteria from the International Panel on Diagnosis of Multiple Sclerosis (Polman et al., 2011). Science breakthroughs in the last 7 years indicate that they may no longer give the most up-to-date advice. The International Panel on Multiple Sclerosis Diagnosis evaluated the McDonald criteria in 2010 and proposed modifications. The 2017 McDonald criteria continue to apply largely to individuals with a typical clinically isolated syndrome, describe what is required to fulfill the propagation of lesions in the brain in time and space, and emphasize the necessity for no other explanation for the presentation. The following changes were made: the presence of CSF-specific oligoclonal bands allows a diagnosis of multiple sclerosis in patients with a typical clinically isolated syndrome and clinical or MRI demonstration of dissemination in space; symptomatic lesions can be used to demonstrate dissemination in space or time in patients with supratentorial, infratentorial, or spinal cord syndrome; and cortical lesions can be used to demonstrate dissemination in space (Thompson et al., 2017).

4.6 Investigations

Multiple sclerosis is diagnosed when a patient presents with acute (relapsing) or insidious (progressive) neurological symptoms (Sand, 2015). All suspected MS patients should have

a lumbar puncture to confirm the clinical diagnosis, rule out MS mimics, and establish a baseline prognostic profile (Dobson & Giovannoni, 2018).

4.6.1 Serological investigation

Depending on the clinical presentation, a conventional baseline profile should include antinuclear factor, vitamin B12, thyroid function, syphilis and HIV-1 serology, as well as antiaquaporin-4 and antiMOG antibody screening.

4.7 MRI

MRI imaging of the brain and spinal cord is important to confirm the diagnosis of MS. Imaging has two functions: it can confirm the diagnosis as well as exclude MS mimics. Incidental nonMS related findings picked up by MRI are nearly 2%, which include pituitary adenomas, pineal cysts, vascular malformations, benign meningiomas, and prolapsed intervertebral discs. Normal electrophysiology can aid in actively eliminating or diagnosing MS by measuring visual, auditory, and sensory evoked potentials and central motor conduction times.

4.7.1 Imaging features

Multiple sclerosis brain lesions are generally ovoid, well confined, perpendicular to the ventricles, and occur in distinct locations: periventricular, juxtacortical, and infratentorial (Sand & Lublin, 2013). Spinal cord lesions are also finely circumscribed, smaller (usually two or fewer vertebral segments in length), fill less than half of the cross-sectional cord area, and frequently involve the dorsolateral cord (Tartaglino et al., 1995). NMOSD (neuromyelitis optica spectrum disorder) is indicated by lesions that are at least three vertebral segments long.

4.8 Treatment

MS treatment can be divided into two categories: disease-modifying therapies, which are often MS-specific and symptomatic therapies, which are used to alleviate symptoms caused by neurological dysfunction (Dobson & Giovannoni, 2018).

4.8.1 Disease modifying therapies

Early MS therapy to prevent long-term impairment has gained popularity as the availability and effectiveness of disease-modifying medications have expanded. A promising treatment for MS is immune reconstitution therapy (such as alemtuzumab and cladribine), which can be administered in brief courses to induce long-lasting immunological effects. Various immune modifying drugs that are used to treat the symptoms of MS (Howard et al., 2016) are shown in Table 5.1 below.

Table 5.1 Various immune modifying drugs used to treat the symptoms of MS.

S. No.	Symptom	Drugs used for treatment
01.	Fatigue	Modafinil, amantadine, stimulants, SSRIs
02.	Depression	SSRIs, SNRIs, bupropion, psychotherapy
03.	Walking difficulty	Dalfampridine (Ampyra)
04.	Nystagmus	Baclofen, clonazepam, gabapentin, memantine
05.	Spasticity	Baclofen, Zanaflex, benzodiazepines, botulinum toxin
06.	Bladder dysfunction	Oxybutynin, terazosin, desmopressin, intravesicular botulinum toxin type A, self-catheterization
07.	Pain or paresthesias	NSAIDs, anticonvulsants, antidepressants, surgery for trigeminal neuralgia
08.	Tremor	Anticonvulsants, propranolol, clonazepam, deep brain stimulation
09.	Pseudobulbar palsy	Dextromethorphan or quinidine (Nuedexta)
10.	Sexual dysfunction	Phosphodiesterase 5 inhibitors (Sildenafil)

4.8.2 Symptomatic treatments

Symptomatic therapies are pharmacological and physical treatments that are used to treat symptoms caused by central nervous system injury. They include anticholinergics for bladder dysfunction and medication for neuropathic pain. Cognitive impairment in MS is complicated and necessitates a tailored strategy. Many symptomatic medications for MS have been approved, including sativex for spasticity and fampridine for walking issues. Sleep is a crucial element of symptomatic therapy, with anxiety, sadness, and weariness being more frequent in people who sleep poorly.

4.9 Management of comorbidities that contribute to long-term impairment

MS impairs brain function and cognitive reserve, resulting in age-related deterioration. MS symptoms might be exacerbated by comorbid conditions and recurring infections. Changes in lifestyle and wellbeing are critical for overall health. Exercise should be encouraged, although intense activity should be avoided during a relapse. According to the WHO, no more than 5% of daily calories should be ingested as sugar. A balanced diet rich in unprocessed foods is suggested in general.

5. Role of medicinal plants in treating multiple sclerosis

Current therapeutic methods for MS regulate the immune system to mitigate the symptoms; however, all standard pharmacological medicines have possible side effects. Treatment failure is typical for people in the chronic or severe stages of the disease. As a result, the use of complementary and alternative medicine (CAM) in MS patients has

skyrocketed, with medicinal plants being the most popular kind of CAM. The efficacy of medicinal plants and their bioactive components in the management of Multiple Sclerosis (MSs) problems is being explored. Several medicinal plants have been shown to have beneficial effects on MS, including *Andrographis paniculata*, *Boswellia papyrifera*, *Ruta graveolens*, *Camellia sinensis (Green Tea)*, *Panax ginseng*, *Aloysiacitrodora*, *Ginkgo biloba*, *Oenothera biennis*, *Cannabis sativa*, *Oleanolic acid*, *Hypericum perforatum*, *Pterodonemarginatus Vogel*, *the compounds curcumin*, *Resveratrol*, *Radix sophorae*, *the drugs Bu Shen Yi Sui Capsule*, *Hyungbangpaedok-san*, *Blueberry*, and *Flavinoids* (Sani et al., 2016).

5.1 Andrographis paniculata

Andrographis paniculata or King of Bitters' is a medicinal plant native to Southeast Asia. It contains andrographolide, which plays a key role in enhancing the immune response (Burgos et al., 2009). It is a neuroprotective substance with antioxidant effects in brain tissue that prevents neurodegeneration. It has been shown to have a positive impact in a preclinical model of autoimmune encephalomyelitis (Burgos et al., 2009; Iruretagoyena et al., 2005) which is achieved by inhibiting T-cell function, dendritic cell maturation, and direct antibody reactivity to myelin antigens (Iruretagoyena et al., 2005).

5.2 Boswellia papyrifera

The antiinflammatory and antiarthritic qualities of Boswellia resin, often known as olibanum or frankincense, have been utilized in medicine since ancient times (Siddiqui, 2011). It also has neuroprotective properties and has been shown to ameliorate MS consequences such as cognitive impairment and gadolinium-enhancing lesions (Sedighi et al., 2014; Sturner et al., 2014).

5.3 Ruta graveolens

Ruta graveolens-family Rutaceae is an evergreen shrub with a distinct aromaticity. It possesses a wide range of biological activities, including antiinflammatory, antirheumatic, analgesic, and antioxidant characteristics, making it a promising choice for the treatment of symptoms like Scotoma induced by demyelinating illnesses or nerve fiber injury.

5.4 Ginkgo biloba

Ginkgo has long been reported to have a promising role in the regulation of cognitive and neurologic diseases in patients with memory loss, Alzheimer's disease, dementia, idiopathic cognitive impairment, and aging. This natural medication has been authorized by the German Commission E for the symptomatic treatment in concentration, memory, and depression (Diamond et al., 2000). EGb 761 is a standardized ginkgo extract containing 24% ginkgo flavone glycosides and 6% terpenoids that has been shown to improve tiredness, severity of symptoms, and functional performance in MS patients (Johnson et al., 2006).

5.5 Aloysiacitrodora

In conventional medicine, lemon verbena (*Aloysiacitrodora*-family Verbenaceae) is used as a sedative, stomachic, anxiolytic, antispasmodic, febrifuge, and diuretic agent that grows spontaneously in South America and is cultivated in the Mediterranean region. Because of its attractive organoleptic characteristics, it is used as a flavoring agent in teas, infusions, and nonalcoholic beverages, as well as in dietary supplements (Farzaei et al., 2017). Lemon verbena contains antioxidant and antiinflammatory properties, as well as being effective in inflammatory bowel disease, rheumatic illnesses, and oxidative stress-related diseases (Abderrahim et al., 2011; Mauriz et al., 2015). The modulatory impact of lemon verbena supplementation on neuroinflammatory markers in MS patients is substantial (Mauriz et al., 2015).

5.6 Panax ginseng

Panax ginseng is a well-known medicinal herb used to treat mental and physical ailments. It includes ginsenosides, flavonoids, triterpenoids, and polysaccharides. *P. ginseng* contains antihyperglycemic, antidepressant, antifatigue, anticancer, antiobesity, and antioxidant properties that possess a positive effect in the cardiovascular, reproductive, and CNS systems, as per modern pharmacological research (Tapsell et al., 2009). Ginseng has a promising role in regulating tiredness and enhancing quality of life in MS patients (Etemadifar, 2013).

5.7 Green tea

Green tea (*Camellia sinensis*) is the most popular beverage after water and has been consumed for over 4000 years (Sharma et al., 2007). Green tea's major active ingredients include phenolic compounds such as epigallocatechin-3-gallate (EGCG), epicatechin-3-gallate (ECG), epigallocatechin (EGC), and epicatechin (EC). EGCG is a well-known antioxidant and antiinflammatory substance that has been the subject of several studies into its biological activities. Green tea's antiinflammatory ability has been linked to the inhibition of important inflammatory cytokine production, including IL-1b, INFc, tumor necrosis factor (TNF)-a and intrinsic nitric oxide synthase (iNOS) (Khan & Mukhtar, 2007; Yang, 2001). It has been proposed that consuming green tea has both preventive and therapeutic properties for a variety of neurodegenerative illnesses. Polyphenon E, a standardized drug based on 50% EGCG, boosted the amount of N-acetyl aspartate by 10%. This amount of N-acetyl aspartate has been linked to MS severity and neural tissue loss, and its measurement is an important indicator for assessing neuronal function (Enzinger et al., 2003).

5.8 Cannabis sativa

Cannabis sativa L. includes 60 or more cannabinoids, the most important of which are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Cannabinoids appear to

have neuroprotective characteristics, with people suffering from MS symptoms such as pain, spasm, stiffness, urine disruption, and tremor declaring that *C. sativa* helps them manage their symptoms (Guy & Flint, 2003).

5.9 Evening primrose

Evening primrose (*Oenothera biennis*—family Onagraceae) group of n-6 series essential fatty acids is a Central American wild medicinal plant that is used as a natural medication. Traditionally, oil produced from the seeds has been used to treat ailments such as asthma, premenstrual and menopausal syndrome, eczema, and rheumatoid arthritis (Montserrat et al., 2014). Coadministration of a polyherbal composition of hemp seed and evening primrose oil has been shown to enhance clinical symptoms, liver enzyme function, polyunsaturated fatty acid (PUFA) levels, and erythrocyte membrane fatty acid composition in blood serum of MS patients (Firouzi et al., 2013a, 2013b, 2014). Surface membrane enzymes such as delta-6-desaturase (FADS2) and secretory phospholipase A2 (sPLA2) play an important role in the therapeutic benefits of this polyherbal mixture (Firouzi et al., 2015).

5.10 Oleanolic acid

Oleanolic acid (OA) is a naturally occurring pentacyclic triterpene found in a wide range of plants, including *Olea europaea*, pomace olive oil, etc. (Jimene et al., 2005). It possesses antiinflammatory, antitumorigenic, antidiabetic, antiviral, cardioprotective, hepatoprotective, and immunomodulatory activities (Liu, 1995, 2005; Raphael & Kuttan, 2003; Dzubaket al., 2005). Oleanolic acid is an immunomodulatory treatment for MS patients because of its antiinflammatory and neuroprotective properties, which target various cytokines and signaling pathways (Liby et al., 2007; Martin et al., 2010). It has been proven to reduce and limit the severity and progression of experimental autoimmune encephalomyelitis (EAEs) (Martin et al., 2010).

5.11 *Hypericum perforatum* (HP)

HP (St. John's wort-family Hypericaceae) is used in traditional medicine to treat depression and is used as an antioxidant, antiinflammatory, and wound healer. The findings of many studies indicate that HP extract minimize the occurrence and severity of EAE by reducing pathological features (leukocyte infiltration and demyelination) and antigen-specific T-cell proliferation. In this respect, it might be a realistic choice for MS treatment (Nosratabadi et al., 2015).

5.12 Pterodonemarginatus

P. emarginatus is an immunosuppressive, antiinflammatory, antirheumatic, healing agent, tonic, and depurative medicinal herb used in Brazilian traditional medicine. Its

essential oil significantly alleviated neurological symptoms and EAE progression. It suppresses the Th1 cell-mediated immune response, and enhances the Treg response. It also suppresses microglial activation and iNOS expression, which are linked to suppression of axonal demyelization and neuronal death throughout the disease progression (Alberti, 2014).

5.13 Curcuma longa

Curcumin (diferuloylmethane) is a yellow pigment found naturally in the rhizomes of the plant *Curcuma longa* (turmeric) that is commonly found in south Asia (Lodha & Bagga, 2000; Srimal & Dhawan, 1973). It's used in foods as a coloring and flavoring spice, and is been used for centuries to treat inflammatory illnesses and heal wounds. It possesses antioxidant, anticancer, and antiinflammatory effects and is being studied in preclinical studies for the treatment of cancer and inflammation (Araujo & Leon, 2001; Claeson et al., 1993). Curcumin inhibits EAE by increasing the number of $CD4^{+}CD25+$-Foxp3+ Tregs in the lymphoid organs and CNS. It has been found that curcumin modulates $CD4^{+}$ T helper cell responses in EAE (Kanakasabai et al., 2012).

5.14 Radix Sophorae flave

Matrine (MAT) is a quinolizidine alkaloid produced from the plant *Radix Sophorae Flave*. It has been used to treat hepatitis B in clinical studies with great safety (Wang et al., 2013; Liu et al., 2014) and has been found to improve neurological indicators, clinical symptoms, and immunological function, minimize the frequency of recurrence in MS patients (Liu et al., 2013). MAT dramatically raised serum Tregs and the expression of Foxp3, a Treg transcription factor, in the spinal cord, as well as enhancing the CNS expression of Nrf2 and HO-1, both of which contribute to the inhibition of oxidative stress and CNS inflammation (Liu et al., 2014).

5.15 Bu Shen Yi Sui Capsule (BSYSC)

BSYSC, originally named Erhuang Capsule, is a phlegm-resolving, yin-nourishing, blood-activating compound used in traditional Chinese medicine. Empirical trials revealed that BSYSC has the capacity to minimize and eradicate symptoms such as limb weakness and paresthesia, minimize the occurrence and severity of relapses, reduce the quantity of medication required, and enhance the quality of life in MS patients (Fan et al., 2006, 2007). BSYSC increased neurological function while decreasing inflammatory cell infiltration and axon and myelin damage in the spinal cord and brain. It suppresses the ratio of CD4 + IL-7+/CD4 + CD25 +FoxP3+ T cells in the spleen and the ratio of IL-17A and FoxP3 mRNA and protein in the brain and spinal cord at various stages. It provided significant neuroprotection to EAE mice. BSYSC's protective mechanisms may be involved in the control of Th17/Tregs (Zheng et al., 2015).

5.16 Hyungbangpaedok-san (HBPDS)

Hyungbangpaedok-san (HBPDS) is a traditional medicine made up of 10 herbs: *Ostericum koreanum*, *Bupleurum falcatum*, *Aralia continentalis*, *Schizonepeta tenuifolia*, *Angelica decursiva*, *Saposhikovia divaricata*, *Poriacocos*, *Rehmannia glutinosa*, *Lycium barbarum*, and *Plantago asiatica*. It has traditionally been used to treat individuals with fever and chills, widespread body aches and discomfort, headaches and stiffness, and redness and swelling of the eyes (Park et al., 2012). HBPDS reduces tumor necrosis factor-(TNF-α) and signal transducer and activator of transcription four expression while increasing $CD4^+$ T cell proliferation, which is related to immunomodulatory and antiinflammatory activities. HBPDS may slow the progression of EAE by modulating the recruitment/infiltration and activation of microglia and peripheral immune cells (macrophages, Th1, Th17, and Tregs) in the spinal cord. HBPDS can be used to protect against autoimmune disorders such as MS (Choi et al., 2015).

5.17 Blueberry

It has been shown to reduce disease incidence in a chronic EAE model and improve disease symptoms in a relapsing-remitting model, along with reducing demyelination and TNF-α levels (Xin et al., 2012).

5.18 Flavonoids

Flavonoids such as luteolin and EGCG (Hendriks et al., 2004; Herges et al., 2011) demonstrated exceptional neuroprotective potential in MS by reducing neuroinflammation and axonal damage. Genistein has been associated to an antiALS preventive effect. Epicatechin, 3′-O-methyl-epicatechin kaempferol, quercetin, hesperetin, and their structural counterparts, isorhamnetin and isosakuranetin, have been shown to prevent neuronal death by blocking the JNK pathway and activating caspase-3 (Ishikawa & Kitamura, 2000). EGCG, quercetin, and resveratrol are frequent ingredients in MS supplements and functional foods (Plemel et al., 2015). Hesperidin and naringin have been investigated for MS treatment, and have been shown to provide protection by reducing EAE development and symptoms (Haghmorad et al., 2017).

The research implies that the effect of flavonoids is largely curative rather than preventive. It is advised that an individual take up to 650 mg of flavonoids on a daily basis (Kannan et al., 2018). Further study is needed to understand the factors that influence the results of flavonoid therapies.

6. Conclusion

Traditional herbal medicines and their derived phytochemicals have been identified as a promising alternative therapy for treating autoimmune disorders such as myasthenia

gravis and multiple sclerosis. The potential of these herbs as future medications is growing since they have been found to improve symptoms, quality of life, and disease biomarkers. However, the complexity and empirical nature of traditional medicines present challenges in redefining their efficacy through modern scientific methods. As a result, high-quality studies are required to confirm the efficacy and safety of medicinal plants in treating myasthenia gravis and multiple sclerosis. Clinical studies with specified phytoextracts or phytochemical combinations based on bioactivity and chemical profiling may be useful in such attempts. Excessively simplistic statements about the efficacy of herbal medications should be avoided. Several plant formulations may not always target numerous cellular/molecular targets, but they may represent the advantage of a combination of drugs. To advance phytomedicine research, it is vital to integrate traditional and modern medical practices, encourage collaboration between researchers and practitioners, promote data sharing, and foster global networking.

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CHAPTER 6

Plant-based approaches for treating celiac and Crohn's diseases: Current insights

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1. Introduction

The immune system protects against infections and diseases resulting from bacterial, viral and other causative agents. However, under certain circumstances, the immune system may produce auto-antibodies against its own cells, leading to autoimmune diseases. In such cases, immune responses are dysregulated and attack the body's own tissues, contrary to their traditional function of protecting the host from external pathogens, i.e., the immune system fails to recognize between foreign agents and own body cells. Complex systems of innate and adaptive immunity and their interactions with genes and environmental factors trigger the development of systemic autoimmune diseases (Banchereau et al., 2013). Autoimmune inflammation and damage to tissues are caused by cell-mediated and/or antibody-mediated effector responses (Casadevall et al., 2003). There are two types of autoimmunity: systemic, in which multiple organs are targeted e.g., rheumatoid arthritis, systemic lupus erythematosus, and organ-specific, in which the focus is on a single organ e.g., Graves' disease, type 1 diabetes etc (Casadevall et al., 2003). Autoimmune pathology that is not under control can cause severe disabilities and/or deformities, as well as loss of organ function. Because they last a long time, autoimmune diseases are expensive, hard on people's minds, and hard on the society as a whole. As far as is known there is no cure for these autoimmune diseases, however, symptoms and relapse can be managed. Various antibiotics corticosteroids and immunomodulators are given to subjects but they accompany serious side effects so, the use of natural compounds is in high demand as they are safe and their use has proven to be promising in the treatment for these autoimmune diseases. Historically, medicinal plants and natural products have been used in antiinflammatory treatment, and many new medicines have been discovered from herbal sources, most of which are plant derived secondary metabolites such as quercetin and kaempferol (Hämäläinen et al., 2007) and

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resveratrol (Kundu et al., 2006). Therefore, it is a very important strategic approach to seek effective antiinflammatory inhibitors from medicinal plants.

Autoimmune diseases, such as chronic inflammatory disorders of the gastrointestinal tract, are a major global health concern. These diseases include celiac disease (CD) and inflammatory bowel disease (IBD), which are divided into two groups: Crohn's disease (CRD) and ulcerative colitis (UC) (Cho et al., 2011). This chapter aims to summarize only Crohn's and celiac disease and their plant-based treatments.

2. Crohn's disease (CRD)

Crohn's disease (CRD), also called regional enteritis or ileitis, is a lifelong form of inflammatory bowel disease (IBD). CRD affects any part of the gastrointestinal tract. This condition inflames and irritates the digestive tract, especially the small and large intestines. Symptoms include diarrhea, abdominal pain, abdominal distension, etc (Baumgart et al., 2012). CRD may also lead to some life-threatening complications e.g., chronic inflammation can cause severe obstruction in the small bowel which can also increase the risk for colon cancers and small bowel cancer (Baumgart et al., 2012).

The main cause of CRD is not known, however, it is believed that combined environmental, immune, and bacterial factors in genetically susceptible individuals may be responsible for CRD development (Cho et al., 2011; Dessein et al., 2008). This disease results in chronic inflammation and the body tries to defend the digestive tract by targeting microbial antigens. In CRD individuals may experience immunodeficiency. It is believed that more than 70 genes are involved in individuals with CRD (Barret et al., 2008; Dessein et al., 2008).

Diagnosis and management of CRD involve intestinal biopsies and some imaging techniques (Baumgart et al., 2012). It is estimated that CRD affects about half a million American population including men, women, and children. 47,400 deaths have been reported in 2015 due to inflammatory bowel disease. Moreover, the CRD has been seen more in developed countries than in developing countries (Burisch et al., 2013; Wang et al., 2016). As far as is known there is no cure for this disease, however, treatment will help to improve symptoms or prevent relapse. Corticosteroids are given to newly diagnosed individuals to improve symptoms quickly (Baumgart et al., 2012). Treatment of CRD includes conventional treatment e.g., corticosteroids, antibiotics, and immunosuppressants. Also, their use is often accompanied by various side effects, some of which severe. The term "alternative medicine" is used when medicinal plants are used for the treatment of CRD. Although the number of studies conducted is very small, the results have been promising (Triantafyllidi et al., 2015).

The role of medicinal plants in the treatment of CRD involves the most valuable study conducted, which was the use of mastic gum, *Tripterygium wilfordii*, and *Artemisia absinthium*. The results were promising compared to placebo in causing remission and helping in the prevention of postoperative recurrence. The use of medicinal plant acts through different

mechanisms which include antioxidant activity, antiplatelet activity, immune regulation, or by inhibiting leukotrienes B4 and nuclear factor-kappa B (Triantafyllidi et al., 2015).

2.1 Types of CRD

Crohn's disease has mainly been categorized into four major types according to the location of inflammation in the GI tract. Each type has its own symptoms.

2.1.1 Ileitis

This mainly affects the ileum (the last part of the small intestines).

2.1.2 Ileocolitis

This type affects both small intestines as well as part of the colon. This is the most common type seen.

2.1.3 Gastroduodenal Crohn's disease

This mostly affects the duodenum and stomach and, in this type, nausea, loss of appetite, and sometimes vomiting are noticed if inflammation and irritation occur in the intestines, resulting in the blockade of some parts of the bowel.

2.1.4 Jejunoileitis

This type of CRD affects the jejunum which is the upper portion of the small intestines and inflammation is seen in those areas, resulting in cramps in the stomach after having meals, fistula, and some other symptoms.

2.2 Symptoms of CRD

Symptoms of CRD may flare up occasionally, followed by periods of bad symptoms and no symptoms (remission). Between the periods of remission years or weeks can pass. Individuals with CRD experience symptoms like Chronic diarrhea, feeling of fullness, anal fissures, anal fistulas, rectal bleeding, loss of appetite and weight loss.

In addition to the above symptoms CRD includes symptoms that occur outside the gastrointestinal tract, e.g., renal stones, liver or bile duct inflammation, anemia and skin and joint inflammation.

2.3 Causes responsible for CRD

The actual cause of CRD is not known however, it is predicted that a combination of environmental and genetic predispositions may be responsible for this. Studies have proven a relationship between the immune system and genetic factors in CRD. According to genetic data and direct assessment innate immunity is compromised. When chronic inflammation occurs, it has been seen that adaptive immunity tries to compensate for the deficiency of innate immunity (Braat et al., 2006).

2.3.1 Immune system

Several hypotheses exist that explain the relationship between the immune system and CRD. However, recent hypothesis state that CRD results from malfunctioning of innate immunity where abnormal secretion of cytokines by macrophages occurs, which leads to a persistent microbial-induced inflammatory response in the colon, where a high bacterial load exists. In addition, another study states that the immune system evolves in accordance with the parasites with which it encounters, now that humans are following modern hygiene standards, it has weakened our immune system (Dessein et al., 2008).

2.3.2 Genetics

People with a genetic predisposition are likely to be affected by CRD. It is estimated that over 30 genes are involved in CRD. Both point mutations and frameshift mutations have been noted. The first frameshift mutation associated with CRD was in the gene NOD2 and a variant of this gene has been shown to be involved in small-bowel involvement (Ogura et al., 2001). Several other genes that increase the risk of developing CRD are SLC11A1, IRGM, IL23R, and ATG16L1 (Prescott et al., 2007, 2010; Diegelmann et al., 2013; Chermesh et al., 2007).

2.3.3 Environmental factors

The high incidence of CRD in more developed countries gives an indication of the involvement of environmental factors. Increased consumption of milk proteins and animal proteins is known to be associated with CRD, in contrast people consuming vegetable proteins show a lower risk of developing CRD (Shoda et al., 1996). Smoking is another factor that increases the risk factor of developing CRD (Cosnes et al., 2004). A dramatic increase in CRD cases has been reported in the United States during the time when hormonal contraception was introduced (Lesko, 1985). Diet and stress were once thought to be contributing factors to CRD, but today's medical community is aware that these factors only serve to exacerbate the condition. The drug doxycycline has also been known to be associated with CRD which was proved by one study where doxycycline was given for acne treatment, and a tremendous increase in CRD cases was seen (Lee et al., 2013).

2.4 Management/treatment for CRD

As of now, there is no standard treatment for the disease, and achieving remission is very difficult, but in cases where it is possible, the relapse may be prevented with medication, changing dietary habits, and also changing eating habits (not eating in bulk one time time but rather in small amounts at different intervals of time). For different subjects, circumstances will be different, so accordingly, treatment paradigms will be different. Sometimes subjects go for surgical procedures to remove or repair the affected part of their GI tract however, surgery has not been proven to prevent relapse. CRD involves first treating acute symptoms and then maintaining remission.

2.4.1 Lifestyle changes

Lifestyle changes can reduce the symptoms, which include good hydration, and consuming a good fiber diet while avoiding diets with high polyunsaturated fatty acids and a high protein diet including an animal protein diet. Maintaining a good and balanced diet may help to control the symptoms of CRD. If the patient develops lactose intolerance the physicians suggest avoiding dairy intake (Shoda et al., 1996).

2.4.2 Medication

Antibiotics: Antibiotics help to prevent infections, as some subjects are susceptible to abscesses (pockets of pus) and fistula because of infections, so using antibiotics helps them combat infection. However, it is known that antibiotics change enteric flora and their continuous usage may pose a threat to the overgrowth of pathogens such as clostridium difficile (Shanahan et al., 2002).

Corticosteroids: Corticosteroids help reduce inflammation that occurs due to CRD. When remission of symptoms occurs, treatment helps with maintenance in order to prevent the recurrence of the disease. Prolonged use of corticosteroids has very serious side effects; hence, they are not suggested for long-term use (Hanauer et al., 2001).

Immunomodulators: These drugs reduce inflammation by suppressing the hyperactive immune system, such as methotrexate, cyclosporine, and azathioprine (suggested as a prodrug for 6-mercaptopurine) (Djurić et al., 2018).

Monoclonal antibodies: Some monoclonal antibodies are used, e.g., vedolizumab, ustekinumab, infliximab, adalimumab, and certolizumab (MacDonald et al., 2016).

Biological therapies: Biological therapies are used to prevent side effects caused by prolonged use of corticosteroids. It basically reduces inflammation and helps treat fistula and abscesses.

3. Role of medicinal plants for the treatment of Crohn's disease (CRD)

Patients with CRD undergo induction of remission and maintenance (long-term treatments that a patient may stay on for many years) of the disease. The use of conventional medicines results in many side effects; hence, awareness about the safe use of alternative or herbal therapies that show promising results and have fewer side effects came into existence. Some of the medicinal plants used that have proven to treat CRD are listed below in Table 6.1 (Triantafyllidi et al., 2015).

3.1 Chios mustic gum (pistacia lentiscus-anacardiaceae)

This tree produces a resin called mastic gum, which is known for its antioxidant activity. It behaves like an immunomodulator by acting on peripheral blood mononuclear cells as TNF-α inhibitor and inhibiting the migration of monocytes and macrophages I.e., MIF

Table 6.1 Medicinal plants showing efficacy against patients with active CRD.

Medicinal plant	Number of patients	Comparison	Duration	Remission with CAM (%)	Remission with control agent (%)	Remarks	References
Boswellia serrata extract H15	102	Mesalazine	–	36%	31%	Better results compared to mesalazine	Gerhardt et al. (2001)
Mastic gum	10	Healthy people	4 weeks	Significant reduction of CDAI and of plasma proinflammatory cytokines	Not applied	Effective and safe herbal	Kaliora et al. (2007)
Tripterygium wilfordii	20	Placebo	12 weeks	–	–	Effective for the treatment of mild or moderately active CD	Ren et al. (2007)
Artemisia absinthium	40	Placebo	10 weeks	65%	0%	The available data seem to be promising	Omer et al. (2007)
Artemisia absinthium	20	Placebo	6 weeks	80%	20%	Promising results	Krebs et al. (2010)
Cannabis	30	No	3 months to 9 years	70%	–	Positive effect on disease activity	Naftali et al. (2011)

Adapted from Triantafyllidi, A., Xanthos, T., Papalois, A. & Triantafillidis, J. K. (2015). Herbal and plant therapy in patients with inflammatory bowel disease. *Annals of Gastroenterology, 28*(2), 210–220. http://www.annalsgastro.gr/index.php/annalsgastro/article/download/1934/1510.

stimulator. In one study, subjects with active CRD were given mastic caps (6 caps/d, 0.37 g/cap) for 4 weeks to 10 patients and eight control subjects. It was observed that subjects treated with mastic caps showed a significant reduction in CRD activity index and also plasma IL-6 and CRP levels were reduced (Kaliora et al., 2007).

3.2 Cannabis sativa

It is a herbaceous plant known to prevent inflammation. Previous studies have already proven the role of endogenous cannabinoids in preventing colon inflammation and hence concluded their potential role in treating CRD (Triantafyllidi et al., 2015).

3.3 Tripterygium wilfordii

It has shown its ability to prevent relapse after the surgery. In a study, 45 subjects with CRD were given *Tripterygium wilfordii* and no relapse was observed after surgery. The drug diterpene triepoxide is the main constituent extract procured from Tripterygium wilfordii and has various functions, including antiinflammatory, antiapoptotic, immune modulator, and antiproliferative. In one exploratory study, 20 subjects with active CRD were given chloroform/methanol extract of *Tripterygium wilfordii* (T2) capsules for 12 weeks, and a significant reduction in CRD activity index was seen, and endoscopic improvements were also noticed after 12 weeks (Ren et al., 2007).

3.4 Wormwood (Artemisia absinthium)

It is a herbaceous perennial plant with a peculiar smell. Since ancient times this herb has been used to treat a large number of digestive problems. Various studies were conducted in order to reveal its therapeutic use for treating CRD. In one study, a herbal combination containing wormwood herb (3×500 mg/day) or a placebo was given to 40 CD patients who were taking 40 mg of prednisone daily for at least 3 weeks. Clinical remission was almost complete in 65% of patients after 8 weeks, compared to none in the placebo group. Up until the end of the observation period, this remission persisted. Additionally, it was discovered that wormwood improved patients' quality of life and reduced the need for steroids (Omer et al., 2007).

3.5 Ananas comosus (pineapple)

This is a tropical plant with edible fruit (pineapple). Bromelain is the enzyme present in pineapple that has proteolytic, digestive and antiinflammatory properties that cause the reduction of cytokine levels and inflammatory mediators by leukocytes and GI tract epithelial cells. Thus, treatment with Bromelain helps to reduce the secretion of proinflammatory cytokines and chemokines and hence helps to relieve symptoms in CRD (Hale et al., 2010).

3.6 Plantago ovata (Ispaghul)

This herbaceous plant, which has laxative properties, softens the stools. When consumed, it absorbs water and forms a large mass, hence stimulating the bowel during constipation (Wong et al., 2016).

3.7 Boswellia serrata

This is a large to moderate-sized tree found in a dry and mountainous region. The resin of this tree has great medicinal value. This resin constitutes β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid, which are responsible for inhibiting proinflammatory enzymes. Out of these four Boswellia acids, acetyl-11-keto-β-boswellic acid is the most potent inhibitor of 5-lipoxygenase, an enzyme responsible for inflammation (Siddiqui et al., 2011).

3.8 Hericium erinaceus (lion's mane mushroom)

It is an edible mushroom and contains various phytochemicals, including β-glucan. It helps to regenerate damaged gastric and intestinal mucous membranes, making it effective in treating CRD (Diling et al., 2017).

3.9 Curcuma longa

It has been found that curcumin can reduce oxidative stress and inhibit the migration of neutrophils and inducible nitric oxide synthase in the intestines. It may also improve micro and macroscopic lesions, prevent apoptosis of intestinal cells, and induce the restoration of the mitogen-activated protein kinase immune reaction (Cunha Neto et al., 2019).

4. Celiac disease (CD)

Celiac disease (CD) is also referred to as gluten-sensitive enteropathy or celiac sprue. The CD patients are intolerant to foods containing gluten, e.g., rye, barley, and wheat. Symptoms include abdominal distension, loss of appetite, and diarrhea. CD usually begins between 6 months and 2 years of age; however, it can occur at any age. People with a genetic predisposition are likely to get CD. When gluten-containing food enters the body, a specific immune response is generated, leading to the production of autoantibodies that affect the various parts of the body (Shan et al., 2002). This disease can be present with other autoimmune diseases, e.g., Hashimoto's thyroiditis, and Type 1 diabetes mellitus (Fasano et al., 2006).

Individuals with CD show evidence of inflammation in the small bowel and also shortening of the villi of the small intestine, termed villous atrophy, thus altering the absorption of essential nutrients and leading to recurrent anemia, bloating, weight loss, diarrhea, exhaustion, and other major side effects. Globally, CD incidence varies between 0.6% and 1%, whereas the prevalence varies between regions and nations (Singh et al., 2018).

Since there is no effective treatment as far as is known people strictly adhere to a gluten-free diet, as this helps them recover from symptoms, especially intestinal recovery. If left untreated, it can lead to serious disorders or even intestinal lymphoma. Many processed meals contain hidden gluten as a taste or texture enhancer, making strict adherence difficult. Gluten-free meals are expensive and scarce, which dissatisfies patients. Despite the diet, some individuals with celiac disease experience ongoing symptoms. A new study seeks nondietary solutions for this condition. Herbal and other natural remedies may prevent or cure inflammatory disorders. However, there are limited investigations on naturally produced chemicals and celiac disease therapy. This book chapter presents current facts to encourage researchers to focus more on natural celiac disease treatments.

4.1 Adult clinical manifestations of CD

The average age at which adults are susceptible to celiac disease is about 44 years old (with a wide age range between 14 and 81 years). It is more prevalent in women (3:1), and this has been confirmed even in very young children. 15%–25% of cases are diagnosed in adults over the age of 60, which is a significant number (Sanders et al., 2002). In certain cases, a history of growth retardation or other signs indicating the existence of CD in childhood have been observed. Malabsorption, diarrhea, weight loss, and abdominal distension are less prevalent in adults than in children (Vivas et al., 2008). In Celiac patients, constipation is accompanied by nonspecific gastrointestinal symptoms that strongly overlap with those of functional dyspepsia (FD), irritable bowel syndrome (IBS), and functional diarrhea. Although it occurs in less than 50% of individuals with Crohn's disease, diarrhea is the major symptom. Patients who have CD may typically have a variety of symptoms, including abdominal discomfort (77%), abdominal distension (73%), chronic diarrhea (52%), constipation (17%), and/or the existence of an alternating bowel movement pattern in an intermediate number (24%). These symptoms are also typical of irritable bowel syndrome (IBS). This suggests that irritable bowel syndrome (IBS) is the initial diagnosis for many people before the discovery of celiac disease (CD) some years later (Nisihara et al., 2016; Sanders et al., 2003).

Celiac disease should be suspected whenever a patient experiences the symptoms of gastroesophageal reflux disease (GERD) that do not improve with antisecretory medications. For instance (Nachman et al., 2011), conducted research in Argentina to determine the presence and severity of GERD symptoms in adult patients at the time of CD diagnosis. They found that adult patients had a significantly higher mean score of reflux symptoms in comparison to healthy controls. In terms of symptoms present at the time of diagnosis, 30.1% of CD patients had moderate to severe GERD, whereas only 5.7% of people without celiac disease had it (Nachman et al., 2011). Usai et al. (2008) conducted a case-control study in patients with CD and concurrent GERD. The results of this investigation showed that the gluten free diet (GFD) alleviated symptoms and was

an effective approach for preventing recurrences. When it comes to adult patients, extra-intestinal symptoms have an exceptionally high incidence, particularly if a specific search for them is conducted. In adults, CD may express itself most commonly as anemia, which is mostly brought on by iron deficiency, osteoporosis, dermatitis herpetiformis, recurrent aphthous stomatitis, and a variety of other neuropsychiatric diseases (Crowe et al., 2011). Some children and adults with CD show no symptoms at all, while others have mild, nonspecific symptoms; nonetheless, serological testing has increased the chance of diagnosing CD in both groups. This is especially true in the families of patients with CD (Reilly et al., 2012).

4.2 Causes responsible for celiac disease

Research suggests that celiac disease only occurs in people who have certain genes and consume food that contains gluten. Experts are studying other factors that may play a role in causing the disease.

4.2.1 Genes

The two main genes involved in celiac disease are:

HLA-DQ2

HLA-DQ8

About 96% of people diagnosed with celiac disease have one or both of these genes (Greco et al., 1998). Certain subsets of the HLA-DQ2 gene can increase or decrease risk. Researchers are studying other genes that may increase the chance of developing celiac disease in people who have DQ2 or DQ8. HLA genes are part of what's called the human leukocyte antigen complex. They help our immune system distinguish between good proteins and those made by infectious agents (viruses, bacteria).

In celiac disease, these genes are faulty. They make the immune system misidentify a protein in gluten-called gliadin-as an infectious agent (Beenhouwer et al., 2018). That is why our immune system attacks villi as they absorb gluten.

4.2.2 Gluten

In celiac disease, the gluten we eat triggers white blood cells to attack the tiny, finger-like projections called villi that line the small intestines. Eventually, the villi erode away. But not everyone who consumes gluten and carries the DQ2 or DQ8 gene variants gets celiac disease. According to research, children with a genetic propensity for celiac disease may be more likely to develop the condition if they consume more gluten during their early years (Silano et al., 2016).

4.2.3 Other factors

Additional variables under investigation may raise a person's risk of celiac disease. For instance, research indicates that the risk may be increased by specific digestive system

illnesses and a higher number of infections in early life. Additionally, according to experts, modifications to the microbiome-the bacteria in the digestive tract that aid in digestion could contribute to the emergence of celiac disease.

4.3 Diseases associated with CD

The extraintestinal ailments most frequently linked to CD include dermatitis herpetiformis, type 1 diabetes, osteoporosis, thyroid disorders, and iron deficiency anemia (Rodrigo et al., 2006). Patients with CD typically experience autoimmune diseases 3–10 times more frequently than people without CD. To explain why autoimmune illnesses are more common in people with celiac disease, some theories have been proposed. One of them is that a longer period of gluten exposure before diagnosis can be a risk factor for the emergence and development of associated disorders (Ventura et al., 1999). Other researchers found, however, that the length of gluten consumption was not related to the existence of autoimmune disorders in patients with a late diagnosis of CD (Guidetti et al., 2001). From an immunological viewpoint, CD is distinguished by an overexpression of interleukin-15 (IL15) at the level of the small intestine's mucosal surface. There is some evidence for its significance in the relationship with autoimmune diseases because, as a result of these elevated cytokine levels, the effector T cells in the intestinal epithelium are not suppressed by the regulatory T cells, which would result in a reduction in gluten tolerance and a rise in the auto-antibodies directed against the target auto-antigens. Another component that has been linked to the development of autoimmunity in CD is vitamin D deficiency. This is because individuals with CD and other autoimmune diseases typically have lower levels of vitamin D in their blood. Even in the presence of numerous malignant tumors, vitamin D plays a significant biological inhibitory role in the regulation of inflammatory hyperactivity. Its true function and the nature of the mechanism by which it operates are still being clarified.

4.4 Treatment for celiac disease

There is no medication that treats celiac disease. At present, the only treatment for CD is the gluten free diet and there will be actual demand for alternative therapies in the future.

4.5 Gluten-free diet

In order to control the symptoms of celiac disease, a person must follow a diet that excludes any foods containing gluten. In most cases, avoiding gluten-containing meals is enough to alleviate symptoms, restore intestinal health, and prevent additional harm. Although the intestinal lining heals completely in the great majority of children, studies have revealed that this process may be incomplete in many adults, even if symptoms improve. The gluten-free diet must be followed continuously. The small intestine can be damaged by even a small quantity of gluten. This is the case for all people who

have the condition, including those who show no outward symptoms. After a person stops eating gluten, it might take a long time (often over a year) for their antibody levels to return to normal.

5. Role of medicinal plants in the treatment of celiac disease

Medicinal herbs, bioactive substances, and dietary measures have all been demonstrated to be useful in the treatment of celiac disease in recent years (Asri et al., 2021). Therapeutic approaches are shifting as more is learned about the efficacy of nutritional therapy, bioactive chemicals, and medicinal plants in treating a variety of metabolic disorders, including celiac disease.

In the treatment of celiac illness, phytotherapy involves the use of several plants whose purpose is

- Plants that aid in the relaxation of inflammatory bowel irritation and swelling.
- Plants having antiinflammatory qualities that aid in the restoration of the intestinal mucosa.
- Use astringents to manage excessively loose stools.

Among the plants, we can mention the following:

5.1 Althea officinalis (marshmallow)

It has a high concentration of mucilage and is thus useful for soothing mucous membrane inflammation. An additional benefit of marshmallow is increased immunity resulting from increased production of WBCs (Milunovich et al., 2014).

5.2 Glycyrrhyza glabra (liquorice)

This plant's roots have antiinflammatory and antispasmodic effects, making them useful for avoiding or relieving gastric mucosal irritation and cramping (Wahab et al., 2021).

5.3 Matricalia chamomilla (chamomile)

Its antiinflammatory and relaxing effects make it useful for dealing with inflammation, swelling, and discomfort. Additionally, its vulnerary qualities can protect the gut wall from degradation.

5.4 Allium cepa (onion)

Due to the presence of quercetin, it helps to decrease inflammation.

5.5 Valerian officinalis (valerian)

It helps alleviate stress and intestinal muscle spasms.

5.6 Plantago psyllium (pysyllium)

This plant's seeds are high in mucilage. They have the ability to absorb extra water from a highly watery gut with feces, avoiding constipation and softening stools.

5.7 Boswellia serrata (salai)

It has been utilized for hundreds of years in Indian herbal therapies for many inflammatory ailments, such as allergies, asthma, arthritis, and digestive problems, such as irritable bowel syndrome (IBS), Crohn's disease, and Celaic disease. It is hypothesized that Boswellia acts by inhibiting 5-lipoxygenase, thereby reducing leukotriene production and reducing proinflammatory cytokine release.

5.8 Nigella sativa L. (black seeds)

Osman et al. examined the efficacy of black seed oil in treating refractory celiac disease (RCD) patients, who had malabsorptive symptoms and villous atrophy despite at least six to 12 months of gluten-free diet. Black seed oil plus gluten free diet (GFD) immunomodulates refractory CD better than GFD alone, resulting in full histological recovery and considerable serological marker reduction. Black seed oil and GFD may help treat refractory CD patients.

5.9 Echinacea

Echinacea belongs to the family Asteraceae and is a genus with significant immunostimulatory and antiinflammatory effects (Manayi et al., 2015). Polysaccharides, caffeic acid derivatives, and alkyl amides are some of the bioactive chemicals found in Echinacea plants. It has been shown that alkyl amides can suppress the activity of cyclooxygenase and lipoxygenase enzymes.

5.10 Camellia sinensis L. (green tea)

According to Dias et al. (2018) green tea contains Epigallocatechin-3-gallate, a flavonoid that may interact with the primary CD immunodominant peptide (32-mer gliadin) and has an antiinflammatory impact and a variety of health benefits for CD patients.

Also, many other studies have found that medicinal plant compounds reduce celiac disease symptoms through multiple mechanisms. De Stefano et al. (2007) examined how lycopene, quercetin, and tyrosol affected iNOS and COX-2 gene expression in RAW 264.7 macrophages stimulated by IFN-γ and gliadin. These compounds inhibit iNOS and COX-2 gene expression by inhibiting nuclear factor-kappa (NF-κB), interferon regulatory factor-1 (IRF-1) and STAT-1α activation. In a transgenic mouse model of celiac enteropathy, Dias et al. (2021) found that oral administration of green tea catechins reduced villus flattening, crypt hyperplasia, and intraepithelial lymphocyte infiltration in gliadin-treated DQ8 mice. Glutathione-disulfide (GSR) and GSH activity increased DQ8 mice's intestinal nucleophilic tone.

6. Medicinal plants for the treatment of various autoimmune diseases

Natural products have been extensively studied for multiple different ailments, such as cancer, infectious diseases, and autoimmune diseases. Table 6.2 given below lists some of the most important bioactive compounds/herbal plants possessing activity against

Table 6.2 Medicinal plants for the treatment of various autoimmune diseases.

Plants/bioactive compounds	Autoimmune disease	Key results	References
Curcumin	Arthritis	Inhabit NF-Kb activity results in reduction proinflammatory cytokines and also regulates cycloxigenase (COX) and lipoxygenase (LOX) leading to suppression of various proinflammatory mediators	Roa et al. (2007)
Gammalinole-nic acid	Rhematiod arthritis	Suppresses inflammation by acting as competitive inhibitor of prostagladin E2 and leukotrienes	AR Setty et al. (2005)
Thymol	Ulcerative colitis	Reduced stress, prolonged the whole gut transit time, increased abdominal withdrawal reflex, normalized the 5-HT3 AR expression	Tahmasebi et al. (2019)
Geranoil	Ulcerative colitis	Improved stool consistency, reduced tumor necrosis factor-α, interleukin-1β and interleukin −6	Medicherla et al. (2015b)
Ginsenoside	Multiple sclerosis	Reduced the permeability of the blood brain barrier (BBB), regulated the secretion of interferon-gamma and IL-4	Zhu et al. (2014)
Hibiscus sabdariffa (roselle plant)	Type 1 diabetes	Reduced fasting blood glucose level	Yusof et al. (2018)
Thymus vulgaris L.	Type 1 diabetes	Reduced blood glucose and serum lipids in rats	Ekoh et al. (2014)
Withania somnifera (ashwagandha)	Psoriasis, arthritis and rheumatism	Produce immunosuppressive action on B and T cell activity in hyper-immune states	Vetvicka et al. (2011)
Hericium erinaceus	Multiple sclerosis	Accelerate the peripheral nerve cell regeneration and stimulate the NGF synthesis	Ristagno et al. (2014)

different autoimmune diseases. However, difficulties in evaluating the efficacy of these products as well as inadequate information about the mechanism of action are among the reasons for skepticism from both public and professional communities.

7. Conclusion and future perspective

Based on the above data, it seems fair to make a statement that the use of plants/herbals for the treatment of Crohn's disease, celiac disease, and other autoimmune diseases may provide a safe and successful substitute for conventional treatment. In addition, we know the cost of treatment in the cases of Crohn's disease, celiac disease and other autoimmune diseases is increasing day by day, this alternative approach can provide a way for successful and affordable treatment. Moreover, International and government agencies should take serious steps to use these phytochemicals for drug development by providing financial support for such studies. However, as part of its drug discovery process, the pharmaceutical industry frequently solicits purified herbal compounds that possess bioactivity that replicates, albeit exceeds, the bioactivity of the parental herbal extract. An unforeseen but not unexpected scenario in that case is that the purified compounds might be more potent, but at the same time they might also be more toxic than the whole natural extract. Carefully planned dosing studies with suitable modifications in the product following an active collaboration between academia and industry would help further expand the applications of natural products in the treatment of Crohn's disease, Celiac disease and other autoimmune disorders.

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CHAPTER 7

Phytomedicine in the treatment of diabetes mellitus

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1. Introduction

Diabetes mellitus remains a critical medical problem for human beings. Different categories of antidiabetic medications are there in the market for the remedial action, which includes insulin analogs, sulfonylureas, biguanides, dipeptidyl peptidase-4 inhibitors, thiazolidinones, α-glucosidase inhibitors, etc. However, long term treatment and side effect of the available hypoglycemic medications leading toward huge demand for efficacious, decreased side effects and affordable agents for the treatment of diabetic condition. Herbal medicine, phytomedicine or botanical medicine are synonymous, utilizes plants intended for medicinal purposes. The active ingredients of the medicinal plants are directing toward its particular use in diseased condition, may be applied in complex formulation of one or more plants. Phytomedicine can be given as an alternative way to prevent and treat diabetes. They may be regularly used in our daily life in dietary regime or may be used in combination with other antidiabetic agents.

2. Clinical overview of diabetes mellitus

Diabetes mellitus (DM) comprises a group of metabolic disorders that share the common feature of hyperglycemia. DM is currently classified on the basis of the pathogenic process that leads to hyperglycemia.

Type 1 DM is characterized by insulin deficiency and a tendency to develop ketosis. Type 1 DM usually results from autoimmune destruction of pancreatic beta cells; it is also known as juvenile-onset diabetes because its peak incidence is in children and adolescent. Type 2 DM is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and excessive hepatic glucose production.

Other specific types include DM caused by genetic defects (maturity-onset diabetes of the young [MODY] and other rare monogenic disorders), diseases of the exocrine pancreas (chronic pancreatitis, cystic fibrosis, hemochromatosis), endocrinopathies (acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism), drugs (nicotinic acid, glucocorticoids, thiazides, protease inhibitors), and pregnancy (gestational DM).

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3. Prevalence

The prevalence of DM is increasing rapidly; type 2 DM frequency in particular is rising in parallel with the epidemic of obesity. Between 1985 and 2013, the worldwide prevalence of DM has risen more than 10-fold, from 30 million to 382 million cases. The number of people with diabetes rose from 108 million in 1980 to 422 million in 2014. Prevalence has been rising more rapidly in low- and middle-income countries than in high-income countries. Between 2000 and 2016, there was a 5% increase in premature mortality from diabetes. In 2019, diabetes was the ninth leading cause of death with an estimated 1.5 million deaths directly caused by diabetes. Diabetes has steadily increased in India and around the world over the last 3 decades, with India accounting for a sizable portion of the global burden. The prevalence of diabetes in India has risen from 7.1% in 2009 to 8.9% in 2019.

4. Pharmacotherapy for diabetes mellitus

Defects in insulin secretion are the one of the main causes that leads to Diabetes Mellitus. Different classes of antidiabetic pharmacotherapeutic agents have been discovered and their selection for use in management depends on the type of diabetes mellitus, age of individual, response of the person, and other factors. Generally, pharmacotherapy used includes (i) drugs that stimulate or facilitate the release of insulin from the pancreatic β-islet cells, (ii) those that increase the sensitivity of receptors to insulin or reduce insulin resistance, (iii) those that reduce the rate at which glucose is absorbed, and (iv) those that inhibit protein glycation. A brief narrative of the classes of antihyperglycemic drugs with examples is as in Table 7.1 (Raing et al., 2000, pp. 389–398).

Most of these orthodox drugs used are either bedeviled with many side effects such as hypoglycemia, weakness, diarrhea, shortness of breath, fatigue, nausea, dizziness, lactic acidosis, weight gain, increase in LDL-cholesterol levels, hepatotoxicity and kidney toxicity, and lactic acid intoxication or are relatively expensive (Akkati et al., 2011; Philippe & Raccah, 2009). This calls for intensive research to provide needed information, including the efficacy and safety of these medicinal plants.

5. Phytomedicine for diabetes mellitus

Besides modern medication, Herbal medicine is one of the subgroups of complementary and alternative medicinal (CAM) therapies. Many patients consider CAM over conventional therapies due to dissatisfied outcomes from the conventional therapies, higher treatment costs and increased side effects of modern medicines. Therefore, the active ingredients of the medicinal plants are directing toward its particular use in diseased condition, may be applied in complex formulation of one or more plants. The use of

Table 7.1 A brief narrative of the classes of antihyperglycemic drugs with examples.

S.No.	Classes of antihyperglycemic drugs	Example
1	Insulin (several generics)	**a.** Sulfonylureas: Glutril, Tolbutamide, Glibenclamide, Gliclazide, Glibenese, Glurenorm, and Glimepiride. **b.** Biguanide: Phenformin and Dimethylbiguanide. **c.** α-Glucosidase Inhibitors: Acarbose, Voglibose, Miglitol, Emiglitate, and
2	Precose	**a.** Aldose reductase inhibitor: Tolrestat, Epslstat, Alredase, Kinedak, Imirestat, Opolrestat, etc. **b.** Thiazolidinediones: Rosiglitazone, Troglitazone, Englitazone, and Pioglitazone.
3	Carbamoylmethyl benzoic acid	Repaglinide
4	Selective sodium-glucose cotransporter-2 (SGLT-2) inhibitors	Remogliflozin, etabonate (known as 189075; GSK), and Sergliflozin.
5	Glucagon-like peptide-1 receptor agonists	Liraglutide
6	Amylin analogs	Pramlintide
7	Dipeptidyl peptidase-4 (DPP-4) inhibitors	Sitagliptin and vildagliptin.
8	Insulin-like growth factor:	IGF-1.

traditional herbal medicines is more associated with patient conception and less paternalistic compared to allopathic medicine in general (Kesavadev et al., 2017; Vasant More et al., 2017; Bing et al., 2016; Kumar et al., 2016).

More than 400 plant species having hypoglycemic activity have been available in the literature (Patel, Prasad et al., 2012). However, investigating new antidiabetic drugs from natural plants has still been attractive because they contain phytoconstituents that demonstrate alternative and safe effects on the treatment of diabetes mellitus. Most plants contain bioactive components, such as phenolics, glycosides, alkaloids, terpenoids, flavonoids, carotenoids, etc., that have been improved as having antidiabetic activities (Malviya, 2010; Grover et al., 2002). Following Table 7.2 enlisted daily used plants in or as food for treating diabetics.

Table 7.2 Medicinal plants having antidiabetic activity along with part used for medicine.

Name	Scientific name	Part used	Properties
Turmeric	*Curcuma longa*	Roots	Antioxidant, Antibacterial, Hepatoprotective
Bitter gourd	*Momordica charantia*	Fruit	Antidiabetic, Antioxidant, Antilipolytic
Cinnamon	*Cinnamomum zeylanicum*	Leaves, Bark	Antioxidant, Anticarcinogenic
Aloe vera	*Aloe barbadensis*	Leaves	Antiseptic, Anti-inflammatory, Laxative, Antioxidant
Guduchi/Indian bitter	*Tinospora cordifolia*	Root, Stem, Leaves	Antiinflammatory, Immunomodulatory, Hypolipidaemic, Anti-microbial
Vijaysar/kino	*Pterocarpus marsupium*	Heartwood, Exudate resin, Bark	Antioxidant, Anti-diabetic, Aphrodisiacantifungal
Painted spiral vginger/spiral flag	*Costus pictus*	Leaves, Flowers, Rhizomes, Tuber	Carminative, Anti-diabetic, Diuretic, Antioxidant
Gurmar/gymnema	*Gymnema sylvestre*	Leaves, Flowers bark	Astringent, Hypoglycaemic, Diuretictonic
Punarnava/red spiderling/Tarvine	*Boerhavia diffusa*	Roots, Leaves	Antidiabetic, Antioxidant, Hepatoprotective, Anti-fibrinolytic, Diuretic
Margosa/neem	*Azadirachta indica*	Fruit, Seeds, Bark, Leaves, Stem	Antibacterial, Anti-helminthic, Neuroprotective, Hypoglycaemic, Antioxidant
Fenugreek/methi	*Trigonella foenum-graecum*	Seed, Leaf	Antidiabetic, Galactagogue, Immunomodulatory, Hypocholesterolaemic

6. Plants having anti-diabetic activity

6.1 Curcuma longa

Curcuma longa commonly known as turmeric; is a rhizomatous medicinal perennial plant and has a rich history of being used in Asian countries, such as China and South East Asia (Kocaadam and Şanlier, 2017; Chattopadhyay et al., 2004). The most active component of turmeric, curcumin, has caught scientific attention as a potential therapeutic agent in experimental diabetes and for the treatment of the complications of diabetes patients (Perez-Torres et al., 2013) primarily because it is effective in reducing glycemia and hyperlipidemia

in rodent models and is relatively inexpensive and safe (Goel & Aggarwal, 2008; Chuengsamarn et al., 2012). The utility of curcumin has been tested in several in vivo and in vitro models implying insulin resistance; for instance, curcumin reduced insulin resistance in rats with metabolic syndrome (Kelany et al., 2017). Curcumin has shown an inhibitory effect on leptin (a hormone that normally inhibits the appetite, by its actions on the brain, and contributes to insulin sensitivity, among other functions) (Moon et al., 2013) actions and a decrease in its concentration (Jang et al., 2008).

Curcumin has been observed to deal with oxidative stress in models of diabetes mellitus by increasing the activity of antioxidant enzymes such as paraoxonase-1 (Assis et al., 2017; El-Azab et al., 2011), superoxide dismutase 1 (SOD1), catalase (Maithilikarpagaselvi et al., 2016) and glutathione peroxidase (Ma et al., 2017; Harinantenaina et al., 2006) which are key enzymes for the antioxidant defense. Inflammation and oxidative stress are closely related to each other in diabetes, and curcumin has shown the potential to fight against them (Ng et al., 1986).

6.2 Momordica charantia

This plant commonly referred to as bitter gourd is an annual climber having wide array of medicinal uses; however, it is widely known for its use in the management of diabetes. The hypoglycemic ameliorative effects of the fruit extract of the plant are reported to be closely linked to the increase in hepatic glycogen, peripheral tissue's glucose transporter (GLUT-4) expression, and higher insulin sensitivity through downregulating the expression of suppressor of cytokine signaling 3 (SOCS-3) and c-Jun N-terminal kinase (JNK) (Khanna et al., 1981).

Bioactive principles reported to be found in Momordica charantia are charantin, oleanolic, vicine, and momordicin (Paul & Raychaudhuri, 2010). Charantin, a sterol isolated from Momordica charantia seeds, induced hypoglycemic effect by stimulating the release of insulin (Thomas & Duethi, 2001). Its antidiabetic effect is similar to sulfonylurea-like medicines. In a clinical study of people with diabetes mellitus, polypeptide-p obtained from fruit, seed, and tissue exhibited antihyperglycemic effects with no adverse reactions (Qin et al., 2010). Related with type-1 diabetes, polypeptide-p has shown action similar to human insulin in the body and, therefore, may be used as plant-based insulin replacement in patients with type-1 diabetes (Couturier et al., 2011).

6.3 Cinnamomum zeylanicum

Cinnamomum zeylanicum, commonly known as cinnamon displays animated role as a spice, but its essential oils and other components also have significant activities, including antimicrobial, antifungal and antioxidant. Cinnamaldehyde (more precisely transcinnamaldehyde or 3-phenyl-2- propenal) is the main constituent in cinnamon bark oil, whereas, that of leaf oil is eugenol (Li et al., 2012). Cinnamon is reported to reduce blood

glucose through decrease of insulin resistance and upsurge in the rate of hepatic glycogenesis (Mang et al., 2006; Patel, Patel et al., 2012). Cinnamaldehyde possesses antioxidant and antidiabetic properties. Moreover, cinnamaldehyde demonstrated antihyperglycemic and antihyperlipidemic effects (Okyar et al., 2001). The cinnamon extract had a moderate effect in reducing fasting plasma glucose concentration by 10.3%, in the cinnamon group as compared to 3.4% in the placebo group. However, no significant changes in HbA1c, total cholesterol, LDL, HDL or triacylglycerol were reported (Tiwari et al., 2018).

6.4 Aloe barbadensis

Aloe vera is a stemless/short-stemmed succulent plant growing to 60—100 cm tall, spreading by offsets. Aloe vera has been widely grown as an ornamental plant. It applied medicinal plant especially in the cosmetic industry, and antidiabetic medication. This traditional medicinal plant belongs to the family Liliaceae. It is original to Africa and Mediterranean countries. Phytoconstituents in the plant are alkaloids, flavonoids, tannins, phenols, saponins, carbohydrates, vitamins and minerals and several other aromatic compounds (Sangeetha et al., 2011). The sap consists largely of D-glucose, D-mannose, tannins, steroids, phytosterols [lophenol, 24-methyl-lophenol, 24-ethyl-lophenol, cycloartenol, and 24-methylene-cycloartanol], amino acids, vitamins, and minerals. Fresh aloe juice from the inner leaf parenchyma contains 96% water. Aloe vera leaf pulp extract showed antihyperglycemic activity on both types of diabetes in rat models, with the outcome enhanced in type-2-diabetes compared with the positive control-glibenclamide (Gupta et al., 1967). Oral administration of aloe vera was beneficial in lowering blood glucose concentration in diabetic patients.

6.5 Tinospora cordifolia

Tinospora cordifolia has been commonly known as Amrita" or "Guduchi," belongs to the Menispermaceae family. It has been one of the important drugs of Indian System of Medicine. Guduchi is native to India and mainly distributed in tropical areas such as Myanmar and Sri Lanka (Gupta & Gupta, 2009). T. cordifolia, containing polysaccharide isolated from this plant exposed the -cell regenerative properties which could be pointed to develop antidiabetic medicine with few side effects (Ahmad et al., 1989). The aqueous and alcoholic extract of the plant has been shown to improve glucose tolerance in diabetic rats (Chakravarthy et al., 1980).

6.6 Pterocarpus marsupium

Pterocarpus marsupium is a tall tree that belongs to Fabaceae family and distributes in India, Nepal, and Sri Lanka, which is widely used in Ayurveda as Rasayana for the management of various metabolic disorders including hyperglycemia (Benny, 2004). Major

bioactive compounds, such as marsupsin, pterosupin and pterostilbene and flavonoids. Epicatechin, isolated from P. marsupium, showed the ability of regeneration of the cells of the pancreas islets (Al-Romaiyan et al., 2010). Moreover, the aqueous extract of this plant was reported that it could stimulate the secretion of insulin and enhance the glucose uptake, so that it can be considered as antidiabetic medicine (Ashwini et al., 2015).

6.7 Costus pictus

Costus pictus, commonly known as "insulin plant" belongs to the Zingiberacea family. It is widely grown in gardens as ornamental plant in South India and also run wild in many places (Pham et al., 2018). An in vitro study in 2010 showed that Costus pictus extracts could stimulate insulin secretion (Hajare, 2018). *C. pictus* extracts increased the calcium ion [Ca^{2+}] influx into the β-cells of pancreatic islets through the voltage-gated calcium channels. This led to the increase in secretion of insulin from the glucose-unresponsive β-cells in diabetic patients (Hajare, 2018).

6.8 Gymnema sylvestre

Gymnema sylvestre (Gurmar/Madhunashini) is one of the natural herbals that has been extensively used in traditional medicine for almost 2000 years. It is a woody, plant species native to India, particularly in South Indian forests. It is also found in tropical Africa and in Australia as well as in Asia, Malaysia, Japan, Vietnam and Sri Lanka (Smruthi et al., 2016). The main plant parts of Gymnema sylvestre used for herbal preparations are its leaves and roots. Gymnema possesses hepatoprotective and sugar suppressing potential (Porchezhian & Dobriyal, 2003; Shanmugasundaram et al., 1983). Gymnema sylvestre demonstrated improvements in glycogen synthesis, glycolysis, gluconeogenesis, and hepatic and muscle glucose uptake (Sathya et al., 2008; Laha & Paul, 2019). The aqueous extract of G. sylvestre leaf informed hypoglycemic activity (Suriyavathana et al., 2012). The action of Gymnemic acids in diabetic treatment was reported to be able to stimulate pancreatic cell production, thereby increasing insulin production, increase insulin sensitivity and insulin activity, help to control and stabilize blood glucose concentration in the body. Gymnemic acids were also reported to be able to inhibit the absorption of glucose in the small intestine and inhibit the conversion of glycogen to glucose molecules in blood (Keerthana et al., 2013).

6.9 Boerhavia diffusa

Punarnava is a well-known drug obtained from the genus Boerhavia L. (Family: Nyctaginaceae), known to possess important therapeuticproperties. B. diffusa and B. erecta are two similar species which have been found in use as Punarnava in India.

It is an erect, puberulous perennial herb distributed in tropical and subtropical areas. It is found to contain alkaloids, flavonoids, saponins, steroids, glycosides and more polar

compounds like sugar, proteins, minerals and vitamins (Patel & Goyal, 2012). Oxidative stress plays a major role in the development of diabetes complications. Glucose oxidation and subsequent oxidative degradation of glycated proteins during diabetes leads to the formation of free radicals. Also, defective antioxidant stress caused by enhanced cellular oxidative stress and reduced antioxidant potential is common among diabetic patients (Krishnaveni & Mirunalini, 2010). The antioxidant property of the plant may be the reason for its action on β-cell regeneration and antidiabetic activity.

6.10 Emblica officinalis Gaertn

Amla is a very important medicinal plant in the traditional Indian system of medicine the Ayurveda and also in various folk systems of medicine in Southeast Asia. Amla has been used for more than 3000 years in India and according the Ayurvedic principles its regular consumption is considered to be extremely useful in arresting degenerative and senescence process. *Emblica officinalis Gaertn*. belongs to the Phyllanthaceae family, commonly called the Indian gooseberry, amla, and amalaki in Sanskrit. It is widely distributed in most tropical and subtropical countries (Yang & Liu, 2014). *E. officinalis* is reported for its antioxidant, gastroprotective, chemopreventive, hypolipidemic, antiviral, antibacterial, antiulcerogenic, hepatoprotective, cardiotonic, antipyretic, and antidiabetic properties (Akhtar et al., 2011; Shah et al., 2005). Research concludes that amla supplement is effective in reducing the Fasting and PostPrandial blood glucose levels and HbA1c levels (Khosla et al., 2000; Prabhakar & Doble, 2011).

6.11 Azadirachta indica

Azadirachta indica (Neem) is a medicinal plant, used in Ayurveda for treating various diseases, one of which is diabetes mellitus. It is known to possess antiinflammatory, antipyretic, antimicrobial, antidiabetic and diverse pharmacological properties. *Azadirachta indica A. Juss* (Family Meliaceae) is well known in India and its neighboring countries as one of the most versatile medicinal plants having wide spectrum of biological activity. Each part of Neem tree has some medicinal property and thus commercially exploitable. The extract of its leaf has similar effects as the antidiabetic drug glibenclamide. The neem extract can control blood glucose and appears to be helpful in preventing or delaying the onset of diabetes (Fuller & Stephens, 2015).

6.12 Trigonella foenum-graecum

Trigonella foenum, commonly known as fenugreek, is a plant of the Fabaceae family that is native to India, China, and North Africa (Kalailingam et al., 2014). The most studied bioactive compounds from fenugreek with reported hypoglycemic actions are diosgenin (3b-hydroxy-5-spirostene), 4-hydroxyisoleucine, and the soluble dietary fiber fraction of fenugreek seeds (Fuller & Stephens, 2015). Diosgenin in fenugreek is a major aglycone of

saponin, and the reported hypoglycemic mechanisms of its action include renewal of pancreatic β-cells and stimulation of insulin secretion (Jetté et al., 2009). 4-Hydroxyisoleucine is a branched-chain amino-acid derivative that is only found in plants, and it represents the majority of the total content of free amino acids in fenugreek seeds (Fuller & Stephens, 2015). It has been shown that the insulinotropic and antidiabetic properties of 4-hydroxyisoleucine act through stimulation of glucose-dependent insulin secretion and reduction of insulin resistance in muscle and/or liver (Jetté et al., 2009).

7. Conclusion

Plants are natural antioxidants and effective herbal medicines, in part due to their antidiabetic compounds, such as flavonoids, tannins, phenolic, and alkaloids that improve the performance of pancreatic tissues by increasing the insulin secretion or decreasing the intestinal absorption of glucose. Many overthe-counter dietary supplements that still have insufficient medical information and supporting scientific evidence are used in the treatment of patients with diabetes and related metabolic disorders. In majority of the herbal products and secondary metabolites used in treating diabetes, the mechanisms of action involve regulation of insulin signaling pathways, translocation of GLUT-4 receptor and/or activation the PPARγ as well as antiinflammatory and immunomodulatory action.

The knowledge in this field is still limited and further studies into identifying active ingredients of several botanicals and their extracts with reported antidiabetic activity, as well as unveiling their mechanism of action, are needed. Since plants and their extracts constitute numerous active ingredients with unknown effect, caution is needed when interpreting and generalizing antidiabetic properties of such preparations. Synergistic effect of different phyto-derived constituents must also be considered. We must also take into consideration that many phytochemicals taken orally undergo considerable loss of bioactivity. More diabetes research and studies should be considered on the dietary phytochemicals, so that it can be beneficial for the patients having type 2 diabetes mellitus.

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CHAPTER 8

Use of medicinal plants in treating arthritis

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1. Introduction

The word arthritis derived from two Greek words "arthron" which means "joints" and "itis" means "inflammation," refers to inflammation with coexisted pain or structural damage. Over 100 types of arthritis exist and are characterized by pain, stiffness, swelling, decreased function, weakness, deformity, and joint instability. Both osteoarthritis and rheumatoid arthritis are common types of arthritis (Senthelal et al., 2022). According to WHO arthritis is the inflammation or degeneration of one or more joints. It is chronic, inflammatory and systemic autoimmune disorder associated with pain, swelling, stiffness of synovial joints (Smolen et al., 2018; Giannini et al., 2020). Arthritis is also referred as Joint pain that influences the musculoskeletal framework, particularly the joints (Giannini et al., 2020). Globally, RA affects 0.5%−1% of the adult population and is associated with significant morbidity and mortality (Naqvi et al., 2019). Symptoms of the disease usually appear between the ages of 20 and 40 and affect women more often than men, at a ratio of 2−3:1 (Alam et al., 2017). It is the fundamental driver of handicap among individuals more than 55 years old in diverse parts of the world (Alam et al., 2017). The global prevalence of RA was estimated at 0.46% in 1980−2018, according to a recent meta-analysis (Almutairi et al., 2021). The prevalence of RA in different countries across the global is highest in Australia with 2% of RA (Australian Institute of Health and Welfare, 2022), the incidence of RA is estimated from 0.35% in Serbia to 0.9% in Poland and Spain in European countries (Batko et al., 2019; Rossini et al., 2014; Roux et al., 2007; Seoane-Mato et al., 2019; Zlatković-Švenda et al., 2014). whereas the lowest incidence was recorded in Algeria and Egypt (Slimani & Ladjouze-Rezig, 2014). Different factors play a role in determining the incidence of RA in different countries, including genetics, epigenetics, and the environment (Liao et al., 2009; Slimani & Ladjouze-Rezig, 2014; Tobón et al., 2010). A joint is a zone of the body where two bones meet. Joint capacities to permit development of the body parts it unites. Joint pain truly implies irritation of one or more joints. Joint inflammation is as often as possible joined by joint torment. Joint torment is alluded to as arthralgia. In straightforward definition Arthritis is a typical condition that causes agony and aggravation in a joint. Arthritis is of various types like

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seropositive (osteoarthritis, rheumatoid arthritis, gout) and seronegative (ankylosing spondylitis, psoriasis arthropathy, reiter's syndrome, postcolitis arthropathy, juvenile rheumatoid arthritis). A brief about the symptoms, diagnosis and treatment of rheumatoid arthritis has been given in Fig. 8.1.

2. Classification of rheumatoid arthritis

1. morning stiffness in and around joints lasting at least 1 h before maximal improvement.
2. soft tissue swelling (arthritis) of three or more joint areas observed by a physician.
3. swelling (arthritis) of the proximal interphalangeal, metacarpophalangeal, or wrist joints.
4. symmetric swelling (arthritis).
5. rheumatoid nodules.
6. the presence of rheumatoid factor.
7. radiographic erosions and/or periarticular osteopenia in hand and/or wrist joints.

Criteria one through four must have been present for at least 6 weeks. Rheumatoid arthritis is defined by the presence of four or more criteria.

3. Classification of osteoarthritis

Grade 1 (doubtful): doubtful joint space narrowing and possible osteophytic lipping.

Grade 2 (minimal): definite osteophytes and possible joint space narrowing.

Grade 3 (moderate): moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends.

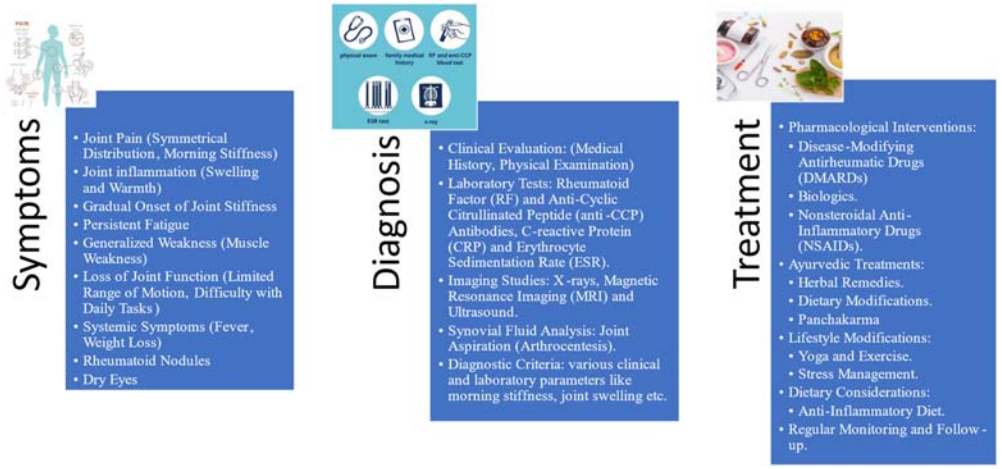

Fig. 8.1 Various symptoms, diagnosis and treatment of rheumatoid arthritis various symptoms, diagnosis and treatment of rheumatoid arthritis.

4. Pharmacology of arthritis

Although there may not be a cure for the arthritis pain, it can be managed to bring the patient relief. Sometimes the pain may go away by taking overthe-counter medication, or by performing simple daily exercises. At times, the pain may be indicative of problems. The major pharmacological agents currently being used for the treatment of RA are the nonsteroidal antiinflammatory drugs (NSAIDs) such as aspirin; the disease-modifying antirheumatic drugs (DMARDs) like methotrexate; the immunosuppressive agents such as prednisone; and the anticytokine agents like antiTNFα receptor antibody (Abramson & Amin, 2002; Kremers et al., 2004; Simon & Yocum, 2000). Acetaminophen, methotrexate or antiinflammatory drugs (ibuprofen), may help ease the pain. Both of these medicines are available over the counter, but stronger doses have been found to have a number of side effects which include stomach ulcers, kidney disease or liver disease (Couzin, 2004; Scheiman, 2001; Simon & Yocum, 2000; Weir, 2002). Topical treatments, such as ointments or gels that can be rubbed into the skin over the affected joint area, may also help ease the pain (Derry et al., 2017). Dietary supplements, like glucosamine, may help relieve the pain (Liu et al., 2018). If those medications or treatments do not ease the pain, supportive aids, such as a brace, cane, or orthotic device in the shoe, can help support the joint to allow ease of movement. Moreover, physical or occupational therapy, antidepressants, steroids, pain killers, Arthroscopy and joint replacement can also be used (Mushtaq et al., 2011). Simple at-home treatments, such as applying a heating pad or ice on the affected area, may be recommended for short periods, several times a day (Freiwald et al., 2021). Soaking in a warm bathtub may also offer relief.

5. Phytomedicine for arthritis

Plants and trees are giving a new lease of life and defining nature in their own way adding new dimensions to healthcare. This is happening through the emphatic emergence of phytomedicine now called Phytomedicine GEN3. The science of plant-based medicines has evolved over the years from age-old Ayurveda. The latest generation of Phytomedicine (as herbal medicines are now being called) are made by extracting medicinal ingredients from herbs in state-of-the-art. In the ever-evolving landscape of healthcare, the intersection of traditional wisdom and contemporary science beckons us to explore novel avenues for managing complex and challenging conditions. Among these, rheumatoid arthritis (RA) stands as a formidable adversary, demanding a nuanced understanding of its intricate pathophysiology and innovative therapeutic strategies. This section embarks on a journey through the diverse realms of medicinal plants, aiming to illuminate their therapeutic potential in the context of rheumatoid arthritis. Various medicinal plants have been evaluated for their potential therapeutic role in rheumatoid arthritis (Table 8.1). Different medicinal plants and the their molecular mechanisms for protecting rheumatoid arthritis has been discussed in this section.

Table 8.1 Medicinal plant (common name, scientific name, part used and active compound) used for treating rheumatoid arthritis.

Common name	Scientific name	Part used	Active compound	Potential benefits	References
Turmeric	*Curcuma longa*	Rhizome	Curcumin	Helps in reducing inflammation and joint pain in RA. Often used in traditional medicine and Ayurveda.	(Dai et al., 2018; Pourhabibi-Zarandi et al., 2021
Ginger	*Zingiber officinale*	Rhizome	Phenolic (Gingerol), Terpene and other antiinflammatory compounds	Known for its antiinflammatory properties, ginger may help alleviate RA symptoms, including joint pain and stiffness.	Aryaeian et al. (2019)
Shallaki	*Boswellia serrata*	Resins	Boswellic acid, Monoterpens, Tetracycline	Reduces inflammation, Improves joint mobility, Reduces pain and stiffness and helps in reducing bursitis.	Siddiqui (2011)
Punnarnava	*Bhorewia diffusa*	Aqueous extract of plant leaves, root	Tannins, Flavonoids, Alkaloids, Rotenoids, Glucosides, Terpenoids	Treats arthritis by reducing inflammation	(Behera et al., 2006; Mishra et al., 2014; Giresha et al., 2017)
Green tea	*Camellia sinensis*	leaf	Polyphenols with antioxidant and antiinflammatory properties.	Some studies suggest that green tea may have a positive impact on inflammatory joint diseases, including RA.	Alghadir et al. (2016), Riegsecker et al. (2013)

Devil's claw	*Harpagophytum procumbens*	Dried roots	Harpagoside, a natural antiinflammatory	Traditionally used to relieve arthritis symptoms, devil's claw may have antiinflammatory effects.	Gxaba and Manganyi (2022), Denner et al. (2007)
Willow bark	*Salix* spp.	bark	Salicin, a natural compound similar to aspirin	Has antiinflammatory and pain-relieving properties.	(Biegert et al., 2004; Lin et al., 2023)
Aloe vera	*Aloe barbadensis miller*	Leaves (colorless mucilaginous gel)	Polysaccharides with antiinflammatory and immune-modulating properties.	May have potential benefits for individuals with RA, but more research is needed.	(Bałan et al., 2014; Cowan, 2010)
Stinging nettle	*Urtica dioica*	roots, stems, leaves and flowers extract	Antiinflammatory substances	studies suggest that stinging nettle may have antiinflammatory effects and could potentially help in managing arthritis symptoms	(Johnson et al., 2013; Riehemann et al., 1999)
Guduchi	*Tinospora cordifolia*	Stem, leaves roots	Tinosporine, Cordifolide, Columbin, Heptacosanol	Treats any kind of fever. Reduces joint pain. Reduces swelling. Treats gouty arthritis.	(Sannegowda et al., 2015; Godbole et al., 2019)
Ajwain	*Trachyspermum ammi*	Seed	Component of thymol which is polyphenol.	Reduces arthritic pain. Treats excess bleeding disorders Improves gut health.	(Korani & Jamshidi, 2020; Sharma et al., 2023)

Continued

Table 8.1 Medicinal plant (common name, scientific name, part used and active compound) used for treating rheumatoid arthritis.—cont'd

Common name	Scientific name	Part used	Active compound	Potential benefits	References
Kalonji	*Nigella sativa*	Seeds and oil	Thymoquinone	Eases joint pains. Increases joint mobility.	(Gheita & Kenawy, 2012; Zielińska et al., 2021)
Haritaki	*Terminalia chebula*	Fruit	Arjungenin, Chebulosides, Tannins, Flavanoids, Alkaloids, Terpenoids, Saponins, Proteins	Mitigates swelling and pain.	(Nair et al., 2010; Moeslinger et al., 2000; Pratibha et al., 2004)
Castor	*Ricinus Communis*	SeedsLeaves	Rutin, Terpenes, Flavonoids, Saponins, Ricin Lepolol, Gallic acid, Thujone	Helps in treating rheumatism.	Hussain et al. (2021)
Ashwagandha	*Winthania somnifera*	Root powder	Flavanoids, Tannins Withanolides, AlkaloidsLactones	Helps to cure joint pain. Treats rheumatoid arthritis and bone health.	Hussain et al. (2021)

5.1 *Curcuma longa* (turmeric)

Curcuma longa L., has been utilized for ages in cooking, as food coloring and ancient medicine globally (El-Saadony et al., 2023). To date, the main focus has been on their antioxidant, antitumor, antiinflammatory, neuroprotective, hepatoprotective, and cardioprotective properties (Zhang & Kitts, 2021). Turmeric contains a yellow-colored polyphenolic pigment named curcuminoids. Curcumin is one of the curcuminoids that possess medicinal properties and can be used for treating inflammation in various health conditions such as cancer, metabolic syndrome, degenerative conditions, and cardiovascular disease (Fu et al., 2017). This compound has excellent antioxidant and antiinflammatory properties (El-Saadony et al., 2023). While there are issues regarding its bioavailability as curcumin is poorly absorbed in the bloodstream. In Ayurvedic practices, the medicinal properties of turmeric help strengthen the overall energy and immunity of the body (Dai et al., 2018; Pourhabibi-Zarandi et al., 2021). Inflammation is generally related to the risk of developing metabolic health conditions or progressing toward severe complications (Chandran & Goel, 2012; Daily et al., 2016). Curcumin present in turmeric is a potent antiinflammatory agent and fights against free radicals, prevents oxidative stress, cellular damage, and reduces inflammation by blocking the inflammatory cytokines like TNF-α, IL-6, COX-2 in rheumatoid arthritis (Kou et al., 2023).

5.2 *Zingiber officinalis* (ginger)

Zingiber officinalis commonly known as ginger, belongs to the family Zingiberaceae. The health-promoting perspective of ginger is attributed to its rich phytochemistry (phenolic like gingerol, terpene and other antiinflammatory compounds) (Mashhadi et al., 2013). The bioactive compounds present in ginger have been found to possess biological activities, such as antioxidant (Nile & Park, 2015), antiinflammatory (Zhang et al., 2016), antimicrobial (Kumar et al., 2014), and anticancer (Citronberg et al., 2013) activities in vitro as well as in vivo models. Ginger has the potential to treat a number of ailments including degenerative disorders (arthritis and rheumatism) (Mashhadi et al., 2013), digestive health (inflammatory bowel syndrome, indigestion, constipation and ulcer) (Zhang et al., 2016), neurodegenerative diseases (Ho et al., 2013), cardiovascular diseases (atherosclerosis and hypertension) (Akinyemi et al., 2015), obesity (Suk et al., 2017), diabetes mellitus (Wei et al., 2017), chemotherapy-induced nausea and emesis (Walstab et al., 2013), and respiratory disorders (Townsend et al., 2013). In arthritis, ginger can be used as drug to treat pain and inflammation due to its antiinflammatory properties which prevent inflammation and pain by inhibiting COX-2 inflammatory cytokines in the body (Al-Nahain et al., 2014; Aryaeian et al., 2019). The bioactive compound in ginger can reduce inflammatory factors hs-CRP and IL2, TNFα, and IL1β gene expression in patients with active RA and it can improve the inflammation in the patients (Aryaeian et al., 2019).

5.3 *Trachyspermum ammi* (ajwain)

Carom seeds, known as ajwain in *hindi*, are always the first choice to deal with stomach upsets. However, these seeds are of great significance for people suffering from arthritis due to their antiinflammatory properties (Korani & Jamshidi, 2020; Sharma et al., 2023). Hence, if you are suffering from arthritic pain or swelling, use carom seeds to get rid of it naturally. *Trachyspermum ammi* is widely used to treat various diseases (Chung et al., 2006). *Trachyspermum ammi* seeds have stimulant, antiseptic, antispam, and antidiarrheal properties (Jeet et al., 2012) and are used as anticorrosive, antiinflammatory (Yu et al., 2016). One of its important components is thymol and isomerism of thymol, called carvacrol are polyphenol compound with antioxidant and antiinflammatory properties, and reduces CRP (C-reactive protein), IL-1β, IL-6, TNF-α, TNF-β, and MMP9 (matrix metalloproteinase 9) levels thus helping in reducing pain in arthritis patients (Korani & Jamshidi, 2020; Sharma et al., 2023). Extract of *T. ammi* seeds given to patients with RA showed a reduction in the expression of *COX2* and *iNOS* genes in the cartilage of RA patients (Korani & Jamshidi, 2020).

5.4 *Boswellia serrata* (shallaki)

This is considered as a potent antiinflammatory, antiarthritic and one of the best analgesic drugs for treating arthritis. Boswellic acid, an active ingredient in shallaki has shown significant pharmacological activity in treatment of inflammatory diseases such as RA, OA, gouty arthritis and bronchitis (Siddiqui., 2011). Gum resin extracts of *Boswellia serrata* have been traditionally used in folk medicine for centuries to treat chronic inflammatory diseases (Kumar et al., 2019; Siddiqui., 2011). The resin's part consists of monoterpenes, diterpenes, tetracycline triterpene acid, β-boswellic acid and acetyl beta boswellic acid. These phytochemicals are responsible for inhibition of proinflammatory enzymes by suppressing interleukin-1 β (IL-1β), tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), and upregulation of the IL-10 production in collagen-induced arthritic rats. These effects of *Boswellia serrata on various cytokines* help reduce pain in patients suffering from arthritis, since these cytokines have a crucial role in chronic inflammation and tissue damage during the progression of RA (Kumar et al., 2019; Zhang & An, 2007; Singh et al., 2013).

5.5 *Bhorevia diffusa* (punnarnava)

Punarnava is a traditional ayurvedic plant that is used to rejuvenate the whole body. The plant as a whole is used in the treatment of rheumatoid arthritis, fever, edema (Behera et al., 2006). Punarnava has powerful analgesic and antiinflammatory properties, which is extremely beneficial in reducing joint and muscle pain, thereby reducing the chances of chronic autoimmune inflammatory diseases like rheumatoid arthritis (Behera et al., 2006; Giresha et al., 2017). A paste of the grounded leaves of this

herb effectively provides relief from the pain and inflammation. Aqueous extracts were prepared from the plant leaves and their activity was determined on subacute inflammation and acute inflammation. Various phytochemicals in the extracts of *Bhorevia diffusa* such as tannins, flavonoids, alkaloids, glucosides, terpenoids, phenolic, rotenoids are responsible for the antiinflammatory properties of this plant (Giresha et al., 2017; Mishra et al., 2014).

5.6 *Ricinus communis* (castor)

R. communis is a tropical flowering plant that is widely cultivated in Asian countries. Studies on *R. communis* leaves have shown antioxidant, antibacterial, osteoarthritic and antiinflammatory activities. *Ricinus communis* commonly known as castor oil plant, is used as a traditional natural remedy or folkloric herb for the control and treatment of a wide range of diseases around the globe. Various studies have revealed the presence of diverse phytochemicals such as alkaloids, flavonoids, terpenes, saponins, phenolic compounds such as kaempferol, gallic acid, ricin, rutin, lupeol, ricinoleic acid, pinene, thujone and gentisic acid (Hussain et al., 2021). These phytochemicals are responsible for its pharmacological and therapeutic effects. *R. communis* has been shown to possess potent antiinflammatory activity (Hussain et al., 2021). Various fractions like ethanolic, methanolic or hexane have been utilized for assessing the antiinflammatory potential of *R. communis*. In one of the studies, the antiinflammatory action of *R. communis* extract was tested by using the hexane, acetone, and methanol fractions. The methanolic extract showed significant antiinflammatory activity which may be due to flavonoids present in it (Nemudzivhadi & Masoko, 2014).

5.7 *Withania somnifera* (ashwagandha)

Withania somnifera (Aswagandha), a small evergreen shrub, is one of them that is known to have therapeutic usage in inflammatory conditions. The herbs are considered safe in India by virtue of their usage for thousands of years in the Indian system of medicine and folklore. Primarily, the roots of *Withania somnifera* are being used for their therapeutic use in the form of whole root powders or extracts. Roots possess antiinflammatory properties and have been extensively researched for their antiarthritis potential (Hussain et al., 2021). Traditionally, it is used in the Indian system of medicine as an antiinflammatory and rejuvenator herb. However, few references are available for its use in other erial parts, especially the leaves, which have antiinflammatory properties and are being studied in the treatment of arthritis. The phytochemical analysis of *W. somnifera* has revealed several groups of bioactive compounds such as flavonoids, tannins, alkaloids, steroidal lactones, and alkaloids. The roots of this plant are considered most active for therapeutic purposes by virtue of the significant accumulation of active constituents, withanolides (Hussain et al., 2021).

5.8 *Terminalia chebula* (haritiki)

Terminalia chebula, also known as Haritaki, is a medium-to large deciduous tree with a height of approximately 30 m and is mainly found in the Indian subcontinent. Its fruits are used in different traditional medicines employed in the treatment of gastrointestinal disorders and inflammatory diseases and for the improvement of immunity (Nair et al., 2010). The fruits of *Terminalia chebula* include tannins, alkaloids, flavonoids, terpenoids, steroids, carbohydrates, proteins, and saponins (Bulbul et al., 2022). A few major phyto-constituents obtained are glycosides, including the triterpenes arjunglucoside I, arjungenin, and chebulosides I and II (Moeslinger et al., 2000; Pratibha et al., 2004). Haritaki is a part of the popular Ayurvedic formulation "Triphala," which is a churna (powder form of preparation) and is used as a remedy for sinusitis, allergies, hemorrhoids, constipation, high levels of cholesterol, and rheumatism, as well as as a tonic for blood purification and malabsorption (Pratibha et al., 2004). Haritaki has also been found to be an antibacterial and an anticonvulsant (Moeslinger et al., 2000; Nair et al., 2010; Pratibha et al., 2004).

5.9 *Nigella sativa* (kalonji)

The black seeds of Nigella sativa are commonly called black caraway. It grows in south Asia and south-west Asia, where the seeds have been traditionally used by the ancient physicians for remedial therapy of several diseases. Many studies have reported that the administration of oil of N. sativa alleviated the symptoms of RA including the inflammation of joints and disease activity score of the patients. Thymoquinone is the major active constituent obtained from N. sativa (Zielińska et al., 2021). It is a bioflavonoid with potential antiinflammatory, antioxidant, neuroprotective, and anticancer activity. Thymoquinone produces antiarthritic effects by reducing articular elastase and myeloperoxidase (MPO) activity. In the arthritic condition of joints, MPO is released from the stimulated granulocytes within the inflamed region and is associated with the activity and accumulation of leukocytes (Gheita & Kenawy, 2012; Zielińska et al., 2021). Thymoquinone is also responsible for hindering the expression of proinflammatory cytokines including IL-1b, TNF-α, IL-10, IFN-c, PGE-2(, and IL-6; these factors are dominantly expressed in the rheumatoid joint and thus play a key role in the pathogenesis of RA. Moreover, Nigella sativa also has a significant property of repairing the cellular impairment caused by the antioxidants by increasing the activity of antioxidant enzymes) (Gheita & Kenawy, 2012; Zielińska et al., 2021).

5.10 *Tinospora cordifolia* (guduchi)

T. cordifolia commonly named as "Guduchi" is known for its immense application in the treatment of various diseases in the traditional ayurvedic literature. *Tinospora cordifolia* is a shrub that is native to India. Its root, stems, and leaves are used in Ayurvedic medicine. Guduchi inhibits COX and LOX synthesis enzymes (Prostaglandins and nitric oxide) and

helps reduce pain and inflammation in muscles and joints (Godbole et al., 2019; Sannegowda et al., 2015). Guduchi controls chronic inflammation and tissue damage by modulating immune response and down-regulating several proinflammatory cytokines including IL-1β, IL6, IL-23, TNF-α and MIP-1. The major constituents present in guduchi are tinosporine, tinosporide, tinosporaside, cordifolide, cordifol, heptacosanol, clerodanefurano-diterpene, diterpenoid-furanolactone tinosporidine, columbin, and b-sitosterol. It has been identified as antispasmodic, antiinflammatory, and antipyretic agent. It is also used in the remedial treatment of RA (Godbole et al., 2019; Sannegowda et al., 2015).

6. Conclusion

Rheumatoid arthritis, characterized by chronic inflammation and autoimmune dysregulation, not only inflicts physical discomfort but also poses a continual puzzle for medical practitioners. While conventional treatments have provided significant strides in managing symptoms and slowing disease progression, the quest for complementary and alternative approaches remains an area of active exploration. Medicinal plants, rooted in centuries of traditional healing practices, have emerged as captivating candidates in this pursuit, offering a rich repertoire of bioactive compounds with the potential to modulate inflammatory pathways, mitigate pain, and contribute to overall well-being. There are numerous plants that have antiarthritic properties at a particular dose. Herbs and species can be used as natural remedies to reduce the inflammation of arthritis. There are many pharmacological therapy options recommended for arthritis that are associated with variable efficacy and safety, especially for the treatment of chronic pain and inflammation. Treatment with herbal medicines may also offer a safer alternative with equal or superior efficacy. The knowledge in this field is still limited, and further studies are needed to identify the active ingredients of several botanical extracts with reported antiarthritic activity. So, the combined approach of scientists, medical practitioners, and researchers is required to make herbal medicine-based treatment more reliable and a certified method for arthritis and many other diseases as well.

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CHAPTER 9

Role of medicinal plants in managing thyroid autoimmune diseases

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1. Background

The endocrine system, which is made up of a network of glands, controls the majority of the body's important processes, ranging from controlling heartbeat to reproduction. The thyroid gland is a crucial part of the endocrine system, which controls a range of biological processes including growth, metabolism, oxygen uptake etc. Thyroid gland secretes Thyroxine (T4) and triiodothyronine (T3) that circulate in the bloodstream and regulate basal metabolic rates, growth, and development. Thyroid dysfunctions can cause a variety of symptoms, such as fatigue, constipation, depression, unexpected weight gain or loss, tremors, irritability, diarrhea, anxiety, and insomnia. With an estimated 42 million cases in India alone, thyroid disease is one of the most significant and prevalent health issues affecting society at large (Unnikrishnan & Menon, 2011). With an estimated 20 million thyroid instances, females are five to eight times more likely than males to have the disease (Sabra & Di Cristofano, 2019).

Nature is full of healing substances, some of which are found in plants. Medicinal plants are a valuable global resource, and due to the numerous negative side effects of synthetic drugs, both developed and developing nations have given much attention to the utility of medicinal herbs for the treatment of various disorders. Herbal plants are great source of prospective medications because they are widely accessible, affordable, effective, safe, and rarely have any adverse effects. Approximately 20% of all known plants have been utilized in pharmaceutical investigations, having a favorable effect on the healthcare system by treating hazardous ailments including thyroid, cardiovascular, cancer and of course diseases relating to the thyroid.

5%–15% of the global population are affected by thyroid illness. Women are three to four times as likely than males to get thyroid illness. Thyroid dysfunction can result from either excessive or insufficient thyroid hormone production known as hyperthyroidism and hypothyroidism respectively or from both conditions.

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Numerous thyroid dysfunctions, viz Hyperthyroidism (Grave's disease) and Hashimoto thyroiditis (Hypothyroidism) are caused by various idiosyncrasies of the thyroid's functioning (Singh et al., 2021). The thyroid is susceptible to autoimmune diseases and dysfunctions due to its intricacy. Body's own thyroid tissue is attacked by immune system in autoimmune thyroid disorder. This can cause the thyroid to stop functioning or perhaps get destroyed. The two pathways underlying autoimmune thyroid disease are as follows.

(1) Autoimmunity caused by T cells is seen in Hashimoto's illness (Rydzewska et al., 2018)

(2) Graves' disease, is characterized by the presence of antithyroid stimulating hormone (TSH) receptor antibodies and humoral response. Both conditions are characterized by thyroid Band T cell infiltration, impaired thyroid function, and thyroid autoantibody synthesis. (Rydzewska et al., 2018)

Most of the Americans who have thyroid disorder have hypothyroidism disorder, which prevents the thyroid gland from producing sufficient thyroid hormone which is necessary for ideal body functioning (Mincer et al., 2017).

Following are examples of the two primary forms of hypothyroidism and hyperthyroidism, each of which has a variety of underlying causes.

Autoimmune (Hashimoto's thyroiditis)	• Common reason for hypothyroidism • Characterized by lymphocyte infiltration of the thyroid, slow death of the gland brought on by cytotoxic T cells, and generation of different thyroid autoantibodies. Occurs when the immune system generates antibodies that attack the thyroid gland, causing severe damage and inflammation.
Central or pituitary hypothyroidism	• This condition develops when the thyroid does not produce required amount of thyroid hormone. It is frequently influenced by environmental and dietary factors, such as vitamin and mineral deficiencies or imbalances, gastrointestinal inflammation, high cortisol levels (caused by prolonged stress or oral steroid use), and/or elevated estrogen. • Hypothyroidism can also result from thyroid surgery (removing a goiter or nodule) or radioactive iodine therapy (to treat hyperactive thyroid,a thyroid nodule, and cancer of surrounding areas).

Autoimmune (Grave's Disease)	• Takes place when the immune system targets TSH receptors, causing thyroid-stimulating antibodies to be produced. Frequently characterized by infiltrative dermopathy and thyroidal hyperplasia (diffuse toxic goiter) (pretibial myxedema)
Central or pituitary hyperthyroidism	• Is caused by the pituitary gland's main overproduction of TSH, which is followed by thyroid hypertrophy and hyperfunction. • Characterized by diffuse goiters, circulating levels of free T4 and T3 that are high, nonsuppressed blood TSH, and clinical thyrotoxicosis

2. Hashimoto's thyroiditis (HT)

Hashimoto's thyroiditis (HT) is an organ-specified autoimmune disorder in which thyroid tissue is attacked by antibodies, preventing production and release of thyroid hormone. In presence of autoantibodies, this condition manifests as lymphocytic infiltration and can result in destruction of thyroid follicular cells, which can result in hypothyroidism. The disease known as hypothyroidism is characterized by insufficient generation of thyroxin and triiodothyronine (T3) hormones from thyroid gland that the body requires for healthy functioning (Akamizu et al., 2017). As the condition worsens, the thyroid gland enlarges, and symptoms include weight gain, exhaustion, constipation, puffy eyes and face, irregular menstruation cycles, etc. HT affects, growth and development, skeletal system, affects the central nervous system, cardiovascular system (CVS), gastrointestinal tract (GIT), and reproductive activities and is most common cause of hypothyroidism observed in 4%–9.5% of the adult population (Bello et al., 2007).

Levothyroxine replacement therapy is the most common form of hypothyroidism treatment nowadays. Levothyroxine replacement therapy can come with some drawbacks, though. Despite being biochemically euthyroid, recent investigations have shown that a considerable proportion of hypothyroid individuals receiving levothyroxine replacement medication had impaired neurocognitive performance and a lower quality of life. Levothyroxine replacement therapy is associated with poor compliance in some patients since it needs lifelong treatment, according to clinical observations (Chakera et al., 2012). Therefore, there is a critical need for more efficient therapeutic methods to treat hypothyroidism (S. Ashwini et al., 2017).

3. Graves' disease

The disease known as hyperthyroidism, often known as a "overactive thyroid," is characterized by presence of excess amounts of free thyroid hormones Triiodothyronine (T3) and/or thyroxine (T4) produced and secreted by the thyroid gland (Iddah et al., 2013).

The most typical autoimmune condition and cause of hyperthyroidism is Graves' disease. The TSH-receptor, which is present on the cell surface membrane of thyroid follicle cells, is complementary to the antigen binding site on the spontaneously produced IgG antibodies made by patients with this condition. These IgG antibodies are referred to as thyroid stimulating immunoglobulins because they bind to the TSH- receptor. The bone marrow, thyroid gland, and lymph nodes all produce TSI. Normally, as we know pituitary gland controls the function of thyroid gland. Thyrotropin receptor antibody (TRAb), an antibody linked to Grave's disease, act likewise pituitary hormone. In other words, the said antibodies over -stimulate the receptor and subsequently trigger follicle cell hypertrophy (toxic goiter), and cause over synthesis/secretion of TH (thyrotoxicosis), which results in a condition known as hyperthyroidism (Nussey et al., 2001). This shows that TRAb disturbs the thyroid's normal regulatory system, which leads to excess production of thyroid hormones. The development of TSI is due variety of genetic variables, including CTLA-4 polymorphisms, and environmental influences (Weetman & A P 2000). Weight loss, heat intolerance, warm, supple skin, elevated heart rate and blood pressure, palpitations, and excessive perspiration are all signs of hyperthyroidism. While the signs of hypothyroidism include puffy eyes and a face, husky voice, delayed speaking, and expressions that are dull (Hughes & Eastman, 2021).

Graves' disease is frequent cause of hyperthyroidism, although there are number of conditions which leads to hyperthyroidism but it is seen that Graves' disease is a frequent cause of hyperthyroidism.

Thyrotropin receptor, Sodium-iodide symporter (NIS) Thyroid peroxidase (TPO), and Thyroglobulin (Tg), are four thyroid antigens known to be targeted by B and T lymphocyte-mediated autoimmunity in Graves' disease (TSH-R). Every antigen performs a particular function. Iodide is transported from blood into colloid tissue by sodium iodide symporter (NIS) and thyroid peroxidase binds iodide to the tyrosine molecule to produce T4; and T4 is then transformed to T3 in the peripheral tissues by iodothyronine deiodinase.

The management of thyroid illnesses continues to be a major priority because of their rising prevalence. There are numerous herbal remedies that provide people with thyroid issues treatment choices, Nevertheless little scientific study has been done in this area, the utilization of herbal products and their biologically active components for the management of endocrine illnesses, such as thyroid problems, has recently attracted increased interest (Kibit et al., 2015).

4. Natural products in medicine and thyroid dysfunction

The world health organization (WHO) estimates that around three-quarters of the global population relies on herbal medicine and other natural therapies (Gilani, 2005). Since ancient times, people have used plants to treat a variety of ailments. People use a variety of plant parts, including the leaves, bark, flowers, fruits, and stalks (Gilani, 2005). The historical use of natural items as therapeutic agents, including plants, animals, and microorganisms, has led to the evolution of the ability to extract active chemical elements from ethnopharmacological plants that aid the discovery of new drugs (Shibata et al., 2012). Natural products differ in their biological activity and drug-like qualities due to their distinct chemical diversity and are one of the most crucial sources for creating new lead compounds. Their effectiveness is correlated with the complexity of their ordered three-dimensional chemical and steric characteristics, which provide numerous benefits in terms of effectiveness and molecular target selectivity. Artemisinin and its analogs are currently used extensively to treat malaria, serving as a successful example of medication creation from natural compounds. This demonstrates how research with natural items has significantly aided in the production of drugs.

The biological system is impacted by a variety of secondary metabolites found in plants, including phenols, phenolic acids, tannins, alkaloids, quinones, flavonoids, terpenoids,coumarins, glycosides, saponins, triterpenoids, and organic acids (Ahmadu & Ahmad, 2021). Plants naturally contain polyphenolic chemicals called flavonoids, which are mostly taken for therapeutic benefits. Numerous flavonoids may impede the function of thyroperoxidase, lowering thyroid hormone levels and increasing TSH and goiter, according to experimental evidence. Flavonoids have been demonstrated to limit cell growth in thyroid carcinoma cell lines, but could also lessen the uptake of radioiodine, which impairs the effectiveness related to radioiodine therapy. Through the inhibition of deiodinase activity or the displacement of T4 from transthyretin, flavonoids also have an impact on the accessibility of thyroid hormones to target tissues. Thus, flavonoids have been demonstrated to interfere with a variety of processes related to the synthesis and availability of thyroid hormones in both in vivo and in vitro models (Santos et al., 2011). Additionally, polyphenolic substances are said to inhibit thyroid peroxidase (TPO), also known as thyroperoxidase or iodide peroxidase, an enzyme that is known to contribute to the synthesis of thyroid hormones (Kowalska et al., 2019).

Thyroxin (T4) and triiodothyronine (T3) serum levels have been shown to be reduced by piperine, the primary alkaloid of *Piper nigrum fruits*. A number of saponins have recently been shown to exert their physiological effects by attaching to nuclear receptors, and thyroid hormone receptors belong to the nuclear receptor family, therefore by attaching to these receptors, saponins can change the action of thyroid hormone (Zhang et al., 2020). Also compounds known to have thyroid-inhibitory characteristics are

p-coumaric acid, Quercetin, cinnamic acid, naringenin, and scopoletin (Sunanda et al., 2020). Consequently, various secondary metabolites have varying effects on thyroid dysfunction.

4.1 Herbs for thyroid diseases

Drug therapy is frequently used to treat thyroid problems. Thyroid hormone replacement is the accepted medical practice for Hashimoto's illness. The conventional recommendations of doctors for Graves' illness include the use of radioactive iodine, antithyroid medications, and procedures to partially or completely remove the thyroid gland. People frequently attempt to seek out complementary and alternative therapies due to the potential negative effects connected with many drugs. A lot of people could go for alternative treatments because of their cultural backgrounds.

The following sections discuss several frequently used natural remedies for Hypothyroidism (Hashimoto's thyroiditis) and Hyperthyroidism (Graves' disease), which are both autoimmune thyroid illnesses.

4.2 Herbs for hypothyroidism

HT may benefit from the use of herbal extracts of guggul, bladder wrack, curcumin, leonurus cardiac, vitex agnus castus, and *iris versicolor*.

4.2.1 Withania somnifera Ashwagandha

One of the most popular herbal remedies in HT is ashwagandha, an adaptogen renowned for its potent immune-modulating and antiinflammatory properties. Promising thyroid-activating ability has also been observed in animal studies, and a recent clinical examination showed how this plant shows activity on thyroid function in patients having bipolar illness. By directly reducing NF—B, it also directly reduces autoimmune and inflammatory diseases (Singh et al., 2021).

4.2.2 Aloe barbendensis

Indices of thyroid function and thyroid peroxidase autoantibodies have been shown to be greatly improved by Miller juice or *Aloe barbendensis*. Additionally, it is known to restore thyrocyte activity, lessen the requirement to convert precursor hormone T4 into active T3, and block deiodination of T4, all of which significantly enhance thyroid activities. Additionally, aloe may help control subclinical hypothyroidism by reducing autoimmune inflammation (Metro et al., 2018).

4.2.3 Nigella sativa (black cumin)

Seeds of Nigella sativa, also known as Black cumin, have significant immune-modulating, antiinflammatory, and antioxidant activities. Thymoquinone, a significant component of black cumin, has been demonstrated to promote thyroid health in animal

models and possesses potential antioxidant and antiinflammatory characteristics. Without affecting the level of serum TSH, black cumin is known to increase T3 concentrations. According to scientists, this is due to its capacity to strengthen antioxidant defense mechanisms, heal the thyroid gland, and resynthesize thyroid hormone. Since it can reduce oxidative stress and thyroid cell destruction while also protecting against hyperplasic alterations of the thyroid parenchyma that take place in thyroiditis, it appears that part of the reason for its therapeutic actions (Singh et al., 2021).

Furthermore, a study found that consuming said plant for hypothyroidism of HT treatment enhanced thyroid function, decreased VEGF, and lessened disease severeness (Farhangi,et al. , 2016). In addition, it is reported to enhance lipid profiles of serum, endothelial dysfunction, oxidative stress, and anthropometric characteristics in Hashimoto cases and can be synergized with levothyroxine to treat metabolic disorders related to Hashimoto thyroiditis (Farhangi & Tajmiri, 2020).

4.2.4 *Triphladya guggulu*

Another possible thyroid stimulant that works without directly affecting the pituitary-TSH axis is triphladya guggulu. Guggul (Commiphora mukul), which has the ability to stimulate the thyroid, lowers LDL levels in hypothyroidism instances. Treatment with guggulu (200 mg/kg/day) for 30 days boost thyroid activities and has antiperoxidative and antioxidant effects by inducing the synthesis of catalase (CAT) and superoxide dismutase (SOD), which aid in the treatment of hypothyroidism (Panda & Kar, 2005). According to reports, *Triphladya guggulu* and Punarnavadi combined therapy improved hypothyroidism and eliminated the requirement to replace hormone in almost 80% of cases treated (Singh & Thakar, 2018).

Intriguingly, polyherbal medicine administered through acupuncture has been shown to have positive effects on boosting T3 and T4 levels in hypothyroidism, increasing levels of glucose, and decreasing triglyceride, total cholesterol, alanine transaminase, and low density lipoprotein levels in hypothyroidism-prone rats. Additionally, the therapy normalized the thyroid hormone imbalance caused by hypothyroidism, stimulated the antioxidation mechanism, and adjusted the TH1/TH2 imbalance, all of which led to histological improvement in thyroid function (Hwang et al., 2018).

Even though hormone replacement therapy is the most frequently prescribed treatment for hypothyroidism and hyperthyroidism, herbal medications are proven to strengthen the immune system and combat thyroid problems.

4.3 Herbs for hyperthyroidism

An overactive thyroid can also be suppressed with the aid of herbs. Although less frequent than hypothyroidism, these herbs are among the best for their antithyroid effects when used as directed. Numerous of these herbs are phenolic acid and their derivative-rich members of the Lamiaceae or Mint family of plants.

4.3.1 Rosmarinic acid

Many plants from the Lamiaceae family like lemon balm (*Melissa officinalis*) rosemary (*Rosmarinus officinalis*) and bugleweed (*Lycopus virginicus*), contain rosmarinic acid. Rosmarinic acid is known to limit peripheral conversion of thyroxine to T3 and to stop immunoglobulin actions on TSH receptors, according to in vivo research. These results imply that rosmarinic acid may help treat Graves' illness. As a result of its ability to guide T cell activity, limit T cell activation and proliferation, alter T cell promotion of proinflammatory cytokine production, rosmarinic acid has been found to have potential applications in autoimmune diseases.

4.3.2 Salvia officinalis

Commonly Known as Sageis another member of Lamiaceae family and shows similar effects as of Rosmarinic acid (Yarnell & Abascal, 2006).

4.3.3 Melissa officinalis (lemon balm)

It is one more quite helpful and secure herb for hyperthyroidism. In addition to its thyroid-blocking properties, it also contains nervine relaxant properties that may be helpful for the anxiety and irritability that sometimes accompany hyperthyroidism. It blocks the enzyme that is necessary for the transformation of T4 to T3, which prevents TSH and thyroid autoantibodies from attaching to TSH receptors (Kaur & Goel, 2011). Additionally, it stops the synthesis of cAMP and is used to treat the tachycardia, insomnia, and hyperactivity that are symptoms of hyperthyroidism. It is well recognized to boost T3, T4 synthesis while lowering TSH levels through feedback inhibition.

4.3.4 Prunella vulgaris (self heal)

One among the plentiful sources of rosmarinic acid (5%) is *Prunella vulgaris* or self heal. After oxidation, this molecule can show self-antithyroid action. Hence, self heal may theoretically possess some antithyroid activity (Mills & Bone, 2000).

4.3.5 Leonurus cardia (Motherwort herb)

Ithigh in quercetin "a flavonoid" and is anadjuvant for overactive thyroid, mainly for hyperthyroidism linked anxiety and palpitations (Wartofsky & Van Nostrand, 2016).

4.3.6 Lycopus europaeus

The use of bugleweed (Lycopus europaeus), a thyroid suppressor, as a therapy option for mild hyperthyroidism has gained widespread acceptance. It has been demonstrated to have potential advantages by stopping the synthesis of TSH, T4 deiodination, and inhibiting iodine metabolism in Grave's disease and preventing thyroid stimulating antibodies (Verma & Jameel, 2012).

4.3.7 *Aegle marmelos*

Scopoletin, a compound obtained from *Aegle marmelos* (Bael/Shriphal), controls overactive by enhancing catalase and SOD activity while decreasing lipid peroxidation. Without generating liver damage, the formulation significantly inhibits hyperglycemia and thyroid function. It is regarded as more efficient than the widely used antithyroid medication "Propylthiouracil" (Panda & Kar, 2006).

Primary ingredient in green tea is catechins, a group of flavonoids that are known to have positive health benefits and also function as an antithyroid agent. Pure catechin taken orally reduces 5′-deiodinase and thyroid peroxidase. Thyroid's physiology is also changed, causing thyroid follicles to enlarge or grow more rapidly, impairing thyroid function and have antithyroid effects (Chandra & De, 2010). Yet, higher doses of catechin in diet can have negative effects and were reported to produce goiter and induces thyroid lesions in rats (Sakamoto et al., 2001).

By normalizing the expression of thyroid peroxidase, thyroxine, T3, thyrotropin, and other cellular antioxidants while maintaining the structural integrity of thyroid tissue, the phenolic compound chavibetol from Piper betel leaves is reported to relieve thyrotoxicosis. The antithyroid potential was found to be in line to that of the widely used antithyroid medicine propylthiouracil (Panda et al., 2019).

Herbal treatment for hyperthyroidism has been touted as a safe, affordable, and effective way to manage thyroid problems.

Much attention and concern is always needed for control and management the thyroid diseases due to increase in its prevalence at alarming and herbal medicines are the best found alternatives.

5. Conclusion

Thyroid problems are the most prevalent endocrine disorders and are exceedingly prevalent. Due to the potential adverse effects associated with many drugs, people frequently turn to alternative therapies, which includes the utilization of herbal medications, for the treatment of thyroid dysfunctions. Hence it is requisite to establish stronger research methods for assessing the positive effects of herbal medications employing various in silico in vitro, and in vivo methodologies. In order to make herbal medicine-based treatment strategies an efficient, trustworthy, and of course accredited therapy method for not just thyroid dysfunctions but other disorders as well, a joint approach of scientists, researchers, and health practitioners is required.

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CHAPTER 10

Role of medicinal plants in autoimmune diseases like Sjogrens syndrome, SLE and Psoriasis: Concept, utilization and perspectives

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1. Introduction

Immune system imbalance is brought on by a variety of chronic illnesses, including cancer, allergies, and autoimmune diseases. In order to produce and employ different plant extracts as a means of preventing human diseases, they have been extracted and changed. Several antibiotics have been created using plant-based chemicals. Humans' immune systems can be stimulated by herbal immunomodulators. Changes in immunomodulatory qualities can be brought on by substances such flavonoids, alkaloids, terpenoids, polysaccharides, lactones, and glycoside derivatives. Plants high in flavonoids, vitamin C, or carotenoids can improve immune function by promoting lymphocyte activity, increasing phagocytosis, and stimulating the generation of interferon. More than 300 plants are said to produce 122 compounds that are utilized economically and have medical properties, such as the coca plant, which is high in cocaine and is used commercially. Digitoxin, a substance found in purple foxglove *(Digitalis purpurea*), is used to treat cardiac issues. Several medications, including caffeine, aspirin, digitalis, morphine, and codeine, are derived from plants. Such medicinal herbs are increasingly being used as immune system modulators in complex immune systems. Immunity is the body's capacity to defend against outside viruses, illnesses, etc. Immunomodulators are substances that regulate our body's immunological response. Immunomodulatory therapy is typically used as an alternative to chemotherapy when immunostimulation and immunosuppression are brought on by conditions like inflammatory illnesses, autoimmune disorders, etc. Many herbs and plants, including *Withania somnifera, Tinospora cardifolia, Magniferaindica, Eclipta alba, Ocimum sanctum, Evolvulusalsinoids, Andrographihis paniculata, Asperagus racemosus,* etc., have been claimed to have immunomodulatory properties. Inflammatory cytokines like tumor

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necrosis factor alpha and chemokine ligand 2 are significant mediators of autoimmune disorders including rheumatoid arthritis and atherosclerosis, respectively, and studies have demonstrated that plant extracts can impact cytokinin activity. TNF-α is thought to be prevented from being released by extracts of plants like *Caryocarbrasiliense*, *Casearia sylvestris, Coccolobacereifera,* and *Terminalia glabrescens*. Similar to that, *Astragalus membranaceus* extract is utilized for enhancing immune function and treating numerous disorders.

2. Sjögren's syndrome

Sjögren's syndrome (SS), also known as "Mikulicz disease," or "dry syndrome," a common connective tissue ailment, both assault and kill the exocrine glands that generate saliva and tears. This chronic systemic autoimmune disorder lacks a known cause. However, xerostomia (oral dryness) and xerophthalmia (medical condition where eyes fail to produce tears) are the results of immune-mediated death of the salivary and lacrimal glands. Dryness can also affect the mucosal surfaces of other organs, including the lungs, gastrointestinal tract, and vagina, leading to a clinical condition described as "dryness syndrome" or "dryness complex". SS can impact practically all organ systems because it is a systemic illness with pleomorphic clinical symptoms. It is very normal for people to feel worn out, sad, anxious, and physically unwell as a result of SS (Negrini et al., 2022).

After rheumatoid arthritis, Sjogren's illness is listed as the most prevalent rheumatic autoimmune condition; its global prevalence rate is in the range of 0.03%−2.7%. There is a growing trend among these patients to adopt interdisciplinary treatments because the majority of existing therapeutic techniques are primarily focused on enhancing the patient's quality of life, with limited efficacy and some common side effects. The pathogenesis of SS is strongly influenced by genetic and environmental factors, viral infection, immune dysregulation, oxidative stress, and inflammation of the lacrimal and salivary glands (Nocturne & Mariette, 2013).

2.1 Epidemiology

The majority of people who suffer from Sjögren's syndrome (SS) are middle-aged women, whereas men experience the disease less frequently (average ratio of women to menis 9:1. The median age of diagnosis of SS is 56 years with another peak occurring between 20 and 40 years. However, the first symptom can appear years before diagnosis. According to a recent meta-analysis, the prevalence of SS was 60.82 per 100,000 population and the pooled incidence was 61 per 100,000 inhabitants, with the highest prevalence encountered in Europe (Qin et al., 2015). Cornec and Chiche examined three reliable epidemiological studies and estimated the total frequency of SS in Europe to be about 39/100,000 (0.04%) (Cornec et al., 2015). Several epidemiological studies indicate that the true prevalence of the disease in the general population ranges from 0.1 to 3 per 1000 people (Negrini et al., 2022).

One of the three most prevalent systemic autoimmune illnesses is assumed to be Sjogren's syndrome. The Sjogren's Syndrome Foundation (2014) estimates that 4,000,000 Americans have SS. Due to the small number of published research, it is challenging to estimate the precise number of afflicted people. Owing to the classification methods utilized, even within a single geographic location, the estimated prevalence of SS can vary greatly. Because of the SS symptoms might coincide with those of numerous other, more well-known autoimmune disorders, SS frequently goes undetected or is incorrectly diagnosed. Since no two SS patients have the same symptoms, diagnosing and treating them can be difficult (Smolik et al., 2017). It may also manifest as a main or secondary disease. In primary Sjögren's disease, the signs and symptoms do not depend on the presence of another disorder. However, in secondary Sjögren's syndrome, symptoms are associated with other autoimmune diseases such as lupus and rheumatoid arthritis (Smolik et al., 2017).

2.2 Pathogenesis

As with other autoimmune diseases, the progression of the SS pathogenesis process is associated with the intervention of several factors like Hepatitis C Virus (HCV), Human Immunodeficiency Virus (HIV), Epstein−Barr virus (EBV), cytomegalovirus (CMV), coxsackievirus, human T lymphotropic virus-1 (HTLV-1), and several others. A virus is suggested as a potential catalyst for disease.as was found during various observations showing that these viruses can cause persistent infection of the salivary glands, cause organ damage and sialadenitis sicca, although these viral infections have There are always distinct clinical features (Del Papa et al., 2021).

Major histocompatibility complex (MHC) class II HLA-DR and HLA-DQ isotypes closely related to SS were discovered by genome-wide association studies (GWAS). The disease is also significantly associated with many nonMHC genes, especially those involved in interferon (IFN) signaling. Therefore, it was hypothesized that specific susceptibility genes may play important roles in activating specific key pathogenic processes in this disease. However, most of these elevated genes, including those associated with activation of the IFN signaling pathway, were not unique to SS and were present in most systemic autoimmune diseases (Vitali et al., 2021). Activated macrophages produce large amounts of inflammatory cytokines, IL-1 and TNFα, causing local tissue damage. Furthermore, inactivated SGECs (salivary gland epithelial cells) triggered apoptotic mechanisms that released autoantigens into the environment via autoantigen-loaded apoptotic vesicles and exosomes. SGECs also function as nonprofessional antigen-presenting cells, as indicated by the expression of class I and class II MHC molecules on their surface. These cells can therefore present self-antigens to immunocompetent cells such as CD^{4+} T cells. These T cells, through subsequent interaction with B cells promoted the production of auto-antibodies by the plasma cells at the end of the B

cell lineage. Environmental stressors may cause salivary gland epithelial cells (SGECs) in individuals with a genetic predisposition by activating a particular Toll-like receptor (TLR). SGECs, when activated, induces the production of multiple chemokines and vascular endothelial factors that are essential for making immune and inflammatory cells such as natural killer (NK) cells, T cells, B cells, and macrophages, that coordinates the entire pathological process of the disease. SGECs are neither passive bystanders nor habitual victims of the inflammatory cascade. Each of these cell types makes a different contribution to the development of inflammatory infiltrates that occasionally take on the appearance of tertiary ectopic germinal centers (teGLCs). Plasmacytoid dendritic cells are stimulated by autoantigen components produced by SGECs (pDCs). These cells, along with SGECs, have the capacity to produce type I IFNs and B-cell activating factor (BAFF). The later cytokine, along with IL-6, is critical for B cell survival and proliferation and may lead to lymphomagenesis in later stages of the disease. Type I IFNs act by triggering the transcription of IFN-associated genes that help in maintaining the inflammatory state in a paracrine and autocrine manner. Dendritic cells (DCs) and helper T cells and other important inflammatory cytokines, including IFN and IL-12, are the major producers and are activated by NK cells. IFN and IL-17, which are both produced by a subtype of Th cell called Th-17, that help to keep macrophages activated and the inflammatory cytokines they release in check. Last but not least, Follicular DCs actively contribute to the organization of inflammatory infiltrates in glandular tissue, leading to teGLC. Mast cells influence local fibrotic changes that contribute to degenerative processes in salivary glands.

Genetic factors are also responsible for causing Sjögren's syndrome and is most commonly associated with HLA DR3 and HLA DR4 alleles. Several studies have proved that the presence of these alleles increases the chances for the development of Sjögren's syndrome. Sometimes immune system also attacks exocrine glands that leads to inflammation and damage. Activation of immune system causes the production of autoantibodies like anti-SSA/Ro and anti-SSB/La antibodies which attacks specific parts of exocrine glands and leads to glandular dysfunction among which lacrimal and salivary glands are most commonly affected which leads to dryness of eyes and mouth. So Sjögren's syndrome is a complex syndrome/complex autoimmune disease which occur due to combined effect of genetic, environmental and immunological factors.

2.3 Treatment

There is no known cure for Sjögren's syndrome but Prednisone, immunosuppressants, and symptomatic therapy are the most commonly used treatments to relieve clinical symptoms and prevent organ damage due to disease progression. Artificial tears and other hydration therapies can treat dry eye symptoms, and corticosteroids and immunosuppressants can be

given to treat more serious problems. These treatments are based on clinician expertize, professional judgment, and sparse clinical research.

To lessen some problems and dry symptoms of Sjögren's syndrome, there are a number of dietary recommendations and herbal remedies for the condition. E.g. For these patients, some suitable meal plans and medicinal herbs are recommended. However, in order to assess their efficacy, clinical studies are needed. Medicinal plants have been used since long times to treat various diseases including autoimmune diseases like Sjögren's syndrome with less side effects, minimal cost, and broad availability because these plants contain various bioactive compounds, which possess anti-inflammatory and antioxidant properties that are beneficial in treating the symptoms of this disease. For example, Licorice is an important herb which have anti-inflammatory properties and is used to increase saliva flow rate, quality of life etc in individuals suffering from Sjogren's syndrome. Likewise, Ashwagandha is used in ayurvedic medicine and is also used to improve the life expectancy of Sjögren's patients. Guggul, Aloe vera are also used to treat many inflammatory conditions in Sjögren's patients. Some more medicinal plants and their medicinal products are mentioned in Table 10.1. Tables 10.2 and 10.3 include some recommendations and treatments involved in treating Sjögren's syndrome.

3. Systemic lupus erythematosus

Systemic Lupus Erythematosus (SLE) is a multisystem autoimmune illness that affects practically all organs and tissues and has a wide range of clinical manifestations. Chronic systemic autoimmune illness SLE is characterized by a propensity for flare-ups (Bertsias et al., 2010). This disease is persistent, difficult to diagnose, and difficult to treat. Although the cause of SLE is unknown, some risk factors that cause immune system dysfunction with antibody production and immune complex deposition have been

Table 10.1 Some useful moisturizing herbal medicines for management of Sjögren's syndrome in TPM (Traditional Persian Medicine).

Scientific name	Common name	Traditional medicinal products
Prunusdulcis	Sweet almond	Boiled fruit wine
Hordeum vulgare L.	Barley	Barley water syrup
Cucurbita pepo L.	Pumpkin	Ointment
Nymphaea alba L.	White water lilly	Oily drop syrup
Malva sylvestris L.	Common mallow	Damp cloth, salve ointment
Descurainia sophia	Fixweed	Beverage
Plantago ovate forrsk	Blond plantago	Mucilage, mouth wash
Prunus domesticus L.	Plum	Laxative

From Minaei, B., Saffarshahroodi, A., Dadmehr, M., & Nimrouzi, M. (2021). The role of diet and medicinal herbs for management of Sjögren's syndrome in traditional Persian medicine. *Iranian Journal of Public Health*, *50*(11), 2358–2360. https://ijph.tums.ac.ir/index.php/ijph/article/download/17120/7429

Table 10.2 Treatment guidelines for systemic manifestations of different symptoms during Sjögren's syndrome.

Dyspareunia	Eat the mixture obtained by soaking the cucumber and pumpkin seeds in goats milk following extraction mixed with quince seeds and sebestan rum boiled in water
Nose dryness	Porridge made with milk starch and almond oil; moisturizing foods and beverages; cooked rice with milk and sugar
Chronic pain	Soft-boiled egg yolk; nutritious soup
Mouth and gastrointestinal dryness	Whey protein; chicken soup; plum soup; barley water
Eye dryness	Avoid wind, dust and sunny weather

From Stefanski, A.L., Tomiak, C., Pleyer, U., Dietrich, T., Burmester, G. R., & Dörner, T. (2017). The diagnosis and treatment of Sjögren's syndrome. *Deutsches Arzteblatt International*, *114*(20), 354–361. https://doi.org/10.3238/arztebl.2017.0354

Table 10.3 Recommendations for the treatment of Sjögren's syndrome.

Indication	Treatment (recommendation)
B Cell lymphoma	Treatment protocols by subentity and stage
Peripheral neuropathy	Antidepressants, gabapentin, corticosteroids - oral or intravenous
Arthritis	Hydroxychloroquine, second line DMARDs as with rheumatoid arthritis
Cryoglobulin emicvasculitis with organ involvement	Methylprednisolone, plasmapheresis, rituximab
Intestinal pneumopathy	Corticosteroids - oral or intravenous, cyclophosphamide in active alveolitis
Tubulointerstitial nephritis	Potassium and bicarbonate replacement
Parotid swelling	NSAIDs and short term oral corticosteroids(<20 mg/day) antibiotic treatment if required

From Minaei, B., Saffarshahroodi, A., Dadmehr, M., & Nimrouzi, M. (2021). The role of diet and medicinal herbs for management of Sjögren's syndrome in traditional Persian medicine. *Iranian Journal of Public Health*, *50*(11), 2358–2360. https://ijph.tums.ac.ir/index.php/ijph/article/download/17120/7429

found. Organ harm brought on by this immune system dysregulation contributes to the disease's varied symptoms and relapsing-remitting history. More drugs are now available to treat this challenging condition that can be used as treatments to reduce organ damage and manage inflammation as a result of new insights into the etiology of SLE. Clinically, lupus is a disorder with an erratic course that includes flare-ups and remissions, where long-term damage has a significant negative impact on quality of life and organ function. The disease can affect a variety of cells, tissues, and organs, and each patient's clinical presentation will be unique. In fact, the clinical picture may change over time, even for the same patient. Joints, skin and mucous membranes, blood cells, brain, and kidney are the organ systems most frequently affected in lupus patients (Fanouriakis et al., 2021).

3.1 Epidemiology

SLE is observed everywhere, with regional variations in incidence and prevalence rates. According to studies, the prevalence rates for SLE range from 20 to 70 per 100,000 person-years, while the incidence rates are from 1 to 10 per 100,000 person-years globally. In the United States (US), the prevalence was calculated to be 1 over 300,000 people, and the incidence across all races was determined to be 5.1 per 100,000 person-years. With a peak female-to-male ratio of 12:1 during the childbearing years, SLE is claimed to primarily affect women (Petri, 2002). The disease also had a restricted gender distribution and can be seen in young children and the elderly. With approximately 10 women suffering with SLE for every man, there is female predominance in the condition (Petri, 2002). The incidence has increased over the past 40 years and ranges from 0.3 to 31.5 instances per 100,000 people annually, most likely as a result of the identification of milder cases (Chakravarty et al., 2007). Globally adjusted prevalence rates are close to or even beyond 50−100 per 100,000 adults (Gergianaki et al., 2017). The severity of the disease might vary depending on ancestry and is typically worse in people of African and Latin American descent. Most patients in Caucasian community are middle-aged women, and about 50% of cases are mild when they first show (Fanouriakis et al., 2021). However, some patients may worsen over time, with one-third of instances in each category being classified as mild, moderate, or severe. In order for a genetically predisposed person to acquire SLE, environmental factors are expected to interact with genetic factors in some way (Fanouriakis et al., 2021). Genetic factors alone are insufficient to explain the start of SLE. Smoking, medications, and ultraviolet radiation are acknowledged environmental variables connected to the etiology of SLE (Bertsias et al., 2010). Infection with the Epstein−Barr virus may be a risk factor for SLE development in the environment, especially in young people (Draborg et al., 2016). Autoantibodies in the sera can appear many years before the onset of lupus clinical symptoms. Epstein−Barr virus infection may result in the generation of interferon alpha, a characteristic of SLE. Many medications, especially those which undergo acetylation, like procainamide and hydralazine, can result in drug-induced lupus, which is typically self-limiting and returns after drug withdrawal. Multiple immune system abnormalities, including altered immunological tolerance, hyperactive T- and B-cells, a decreased capacity to remove immune complexes and apoptotic cells, and the failure of numerous regulatory systems within the immune network, all contribute to SLE (Pathak & Mohan, 2011). Intracellular antigens are released abnormally for instance due to dysregulated apoptosis. Increased autoantibody synthesis brought on by immune complex-mediated type III hypersensitivity reactions is the result of a loss of B-cell self-tolerance. Complement activation, inflammatory cell recruitment and tissue damage results from the accumulation of immune complexes within tissues. With faulty type-1 interferon regulation, innate immune cells are drawn in and stimulated to create harmful

cytokines like interferon alpha, tumor necrosis factor, and interleukin-1. Antigen presentation, T-cell activation, and dendritic cell modulation are additional ways that B-cell engagement might happen without antibody synthesis. With abnormalities in $CD8^{+}$ and T-regulatory cell function happening along with an enlarged CD3 + CD4 -CD8 - T-cell lineage, T cells also play a role in autoimmunity in SLE. There are a number of symptoms associated with lupus. Not everyone with lupus will have the same set of symptoms. Many of these symptoms overlap with other medical conditions. This is one of the difficulties in diagnosing someone suffering with lupus.

3.2 Symptoms

Symptoms of SLE include Joint pain, Muscle pain, Rashes, Fever, Sensitivity to sunlight, Hair loss, Mouth sores, Dry eyes, Fatigue, Chest pain, Stomach pain, Shortness of breath, Swollen glands, Headaches, Confusion, Depression, Issues with the kidneys, heart or lungs, seizures, Blood clots, Anemia.

3.3 Role of plant extracts in treating SLE

Although glomerular nephritis is a significant consequence, patients who acquire lupus nephritis may benefit greatly from botanical medication. Flax seed, which contains anti-inflammatory omega-3 essential fatty acids and phytoestrogenic lignans, is one plant that may have this ability. 26 patients with SLE who were on prednisone participated in a single-blind, randomized clinical trial in which 30 g of flax seeds were given to them each day for a year before switching to a year without the supplement (Clark et al., 2001). Sadly, there were a lot of dropouts and poor follow-up, and just nine patients clearly took the flax seeds as directed. Even so, there were unmistakable signs that the renal function of the nine patients who did consistently consume flax seed had improved. Patients with lupus nephritis may also benefit from immunomodulators.

Medicago sativa is a phytoestrogenic plant that should be avoided in SLE This herb's sprouted varieties contain the arginine homologue canavanine. Limited study has suggested that this drug may cause SLE. The easiest way for people with SLE to avoid canavanine is to refrain from taking alfalfa (Rosenthal & Nkomo, 2000). Traditional Asian medical systems have shown that use of cloud mushroom can improve symptoms in patients suffering from SLE along with cancer and autoimmune diseases particularly in the West.

Sarmepavine, an alkaloid derived from the rhizome of *Nelumbo nucifera* (the lotus), has been demonstrated in studies to decrease the growth of T lymphocytes in a mouse model of SLE. According to (Liu et al., 2006), lotus rhizome extracts, particularly alcoholic extracts, have substantial antioxidant activity that may help mitigate some of the pathologies associated with SLE. Clearly, additional investigation is required to ascertain the full range of action and practicality of this intriguing herb in the treatment of lupus. Studies on animals have demonstrated the immunosuppressive characteristics of the antimalarial drug

artemisinin and its congeners, which are present in the herbs *Artemisia annua* and *Artemisia apiacea* (Tawfik et al., 1990). According to certain preclinical studies, these medications may actually have immunomodulatory effects. The clinical potential of sweet annie for treating SLE is supported by its immunomodulatory ability, together with the historic usage of these herbs for inflammatory disorders. In China, rheumatic autoimmune illnesses including lupus erythematosus and rheumatoid arthritis are frequently treated with *Artemisia annua* L. (Asteraceae), a plant noted for its antioxidant properties and high nutritional value in vitamins and amino acids. Additionally, this herb has anti-inflammatory and immunosuppressive properties (Das, 2012). The majority of CLE (Cutaneous Lupus Erythematosus) patients are treated with antimalarial drugs that are derived from plants (Hejazi & Werth, 2016). Peruvian natives used bark extract from the Cinchona tree (*Cinchona officinalis* L.) to make quinine to treat fevers. Europeans discovered how to make synthetic compounds, such as the hydroxychloroquine (Plaquenil) and chloroquine which are used today to treat patients with cutaneous and systemic lupus (Achan et al., 2011). The fungi *Penicillium stoloniferum, P. brevicompactum, and P. echinulatum* are the sources of the drug mycophenol atemofetil, which is used to treat discoid lupus in addition to a number of other disorders (Allison, 2005).

The medicinal spice known as turmeric, or *Curcuma donga* L. (Zingiberaceae), is well-known for its anti-inflammatory and antioxidant properties. Curcumin (diferuloylmethane), the active component, has a wide variety of bioactive chemicals that are safe and effective against a number of disorders, including autoimmune diseases. Studies have shown that curcumin has a number of potential SLE-friendly modes of action. In both in vitro and in vivo tests, Zhao et al. showed that curcumin decreases proteinuria, renal inflammation, serum anti-dsDNA antibodies, splenomegaly, and NLRP3 inflammasome activation in MRL/lpr mice (Zhao et al., 2019). Although this suppression was not unique to autoimmunity, Kurien et al. found that turmeric significantly reduced the binding of autoantibodies to their relevant antigens by up to 70% in SLE patients. In invitro and in animals, quercetin, a plant polyphenol, has anti-inflammatory, antiviral, antiplatelet aggregation, and capillary permeability characteristics). Using Tartary buckwheat (*Fagopyrum tataricum*) as a source of quercetin, this study shows that it can lower serum antibody levels, CD^{4+} T cell activation, and T-bet expression levels (Li et al., 2016).

4. Psoriasis

An autoimmune inflammatory skin illness with a genetic propensity known as psoriasis is characterized by aberrant angiogenesis, hyperkeratosis, enhanced epidermal proliferation, and cutaneous inflammation. Topical, systemic, photo-therapy, combination, herbal therapy, and new compounds can all be used to treat it (Ayala-Fontánez et al., 2016). Topical medications include retinoids, vitamin D, calcipotriol, corticosteroids, dithranol,

etc. Agents like methotrexate and cyclosporine are ones that are routinely utilized. Examples of photo-therapy include psoralen plus and UV-B. However, these treatments have insufficient efficacy, cause organ damage, etc. A range of substances used in natural treatment, such as linseed oil, fish oil, and methanolic extracts of du Zhong (Eucommiaulmoides), alter T cell and cytokine function at different stages. However, no further in vivo dose and its efficacy data have been established as of yet (Ayala-Fontánez et al., 2016). Hepatotoxicity, nephrotoxicity, and bone marrow suppression are side effects of the prebiologically created systemic medicines that can be avoided with small molecule inhibitors and enzyme inhibitors (Rahman et al., 2012). Around 125 million individuals worldwide are affected by psoriasis, a prevalent chronic inflammatory disease with incidence rates ranging from 0.3% to 0.6% in different racial groups (Arnold et al., 2019). Many people are willing to employ effective alternative therapies, such as Chinese herbal medicine (CHM). CHM contains a number of active substances that are useful in the treatment of psoriasis. Inhibition of immunological responses, aberrant proliferation and differentiation, and oxidative stress are all reduced by CHM molecules (Li et al., 2002). Psoriasis is a widespread inflammatory skin condition with unclear origins that also involves multiple gene inheritance, inflammation, and immunity etc. Many Chinese remedies have been found to have antagonistic effects on inflammatory cytokines including TNF alpha, platelet activating factor, IL8, and others since cytokines are significant psoriasis mediators. It has been observed that Chinese medicines work by inhibiting keratinocyte proliferation and inducing apoptosis in psoriasis patients because they have aberrant keratinocyte proliferation and apoptosis. Psoriasis can be treated successfully with Chinese remedies and certain of its monomers. *Radix Peucedani, Ramulus Visci, Folium Ginkgo,* and other CM monomers have the ability to modulate TNF-alpha, IL8, and other factors that are involved to the pathogenesis of psoriasis. The biochemical basis of psoriasis has been revealed, and it is now known to be an autoimmune disease with serious health consequences that go beyond the skin. Psoriasis comes in a variety of forms, and each one has unique indications and symptoms.

4.1 Different forms of psoriasis

4.1.1 Psoriasis plaque

Plaque psoriasis, the most prevalent type of psoriasis, results in scale-covered, dry, elevated skin patches (plaques). On skin, the plaques may seem thicker, darker, and more purple, gray, or darker brown in hue. Plaques can be found anywhere on the body, but the scalp, knees, elbows, and chest are where they are most frequently found (Wilson et al., 2009).

4.1.2 Nail psoriasis

Pitting, irregular nail growth, and discoloration can all be brought on by psoriasis and affect both fingernails and toenails. The nail bed may become loose and separate from

psoriatic nails (onycholysis). The nail may break if the illness is severe. Whether the hyponychium, nail bed, or nail matrix has been impacted will determine how the nail's morphology alters. The likelihood of nail involvement is higher in people who also have psoriatic arthritis. Kaur et al. (1986) examined 782 psoriasis patients in North India and found that about 1.4% of total dermatology out-patients had Psoriatsis. 75% of patients had over 50% involvement of skin surfaces. 62% of patients have nail psoriasis. The most frequent nail change was pitting, which was closely followed by onycholysis, nail plate thickening, discoloration, subungual hyperkeratosis, and longitudinal ridging.

4.1.3 Guttate psoriasis

Young adults and children are most frequently afflicted by this condition. Usually, a bacterial infection, like strep throat, is what sets it off. Small, drop-shaped scaling lesions on the trunk, arms, or legs are its telltale sign. Skin damage, stress, and even tonsillitis or streptococcal sore throat are common causes of it (Griffiths et al., 2007).

4.1.4 Inverse psoriasis

The groin, buttocks, and breast skin folds are mostly impacted by inverse psoriasis. It results in scaly, inflammatory skin patches that get worse with friction and perspiration. This kind of psoriasis may be brought on by fungi. This kind commonly develops in the groyne, armpits, under the breasts, in skin folds, and in the buttocks and genitalia. Inverse psoriasis frequently has yeast build-up, which can get worse with sweating and rubbing (Micali et al., 2019).

4.1.5 Pustular psoriasis

It is a rare type, causes clearly defined pus-filled blisters. It can occur in widespread patches or on small areas of the palms or soles. Pustular psoriasis appears as raised bumps that are filled with noninfectious pus (pustules). Pustular psoriasis can be localized, commonly to the hands and feet (palmoplantarpustulosis), or generalized with widespread patches occurring randomly on any part of the body. Neutrophils get infiltrated in stratum spinosum and sterile cutaneous pistules arises.

4.1.6 Erythrodermic psoriasis

Erythrodermic psoriasis is a rare type of psoriasis, but it's much more serious than many other subtypes. The plaques can cover almost your entire body, potentially leading to life-threatening problems (Boyd & Menter, 1989). Psoriasis is an autoimmune disease. It happens when one's immune system is inappropriately overly active and causes harm to one's own body. Inflammation from this reaction causes new skin cells to form too fast.

4.2 Prevalence

In the western world, the prevalence of psoriasis is between 2% and 4%, however in India, it is between 1% and 2%. The fact that the disease is becoming more common in emerging nations is especially concerning. Psoriasis is thought to have a multi-factorial pathogenesis and aetiology, involving both innate and acquired elements. Numerous immunological aspects have been taken into account, and many of the most recent medications target these cytokines. Most Indian prevalence studies are conducted in hospitals (Kaur et al., 1986). The comparison data from several epidemiological studies on psoriasis conducted in India are presented in Table 10.4 that compares the data from various Indian epidemiological research on psoriasis. Okhandiar and Banerjee (1963) gathered data from numerous medical colleges in Dibrugarh, Calcutta, Patna, Darbhanga, Lucknow, New Delhi, and Amritsar. They discovered that the overall incidence of psoriasis was 1.02%, with a range of 0.44%–2.2% among all skin patients. They observed that the frequency in Amritsar (2.2%) was higher than in other locations in Eastern India and theorized that this would be due to varying environmental factors (temperature extremes), dietary preferences, and genetic variations. The extremely high male to female ratio (2.46:1) could not be satisfactorily. Highest incidence was noted in the age group of 20–39 years and the mean age of onset in males and females was comparable.

Bedi (1997) reported the prevalence of psoriasis from north India to be 0.8% among the skin patients but he studied very sample size for the study. Male to female sex ratio

Table 10.4 Comparative analysis of psoriasis cases with different parameters by different researchers during 20th century.

	Okhandiar and Banerjee (1963)	Bedi (1997)	Kaur et al. (1986)	Bedi (1995)	Inderjeet Kaur et al. (1997)
Total no. of patients	3573	162	782	530	1220
Prevalence (% of total dermatology outpatients)	1.02	0.8	1.4	2.8	2.3
Male:Female	2.46:1	2.5:1	2.3:1	2.4:1	2.03:1
Mean age in males and females	Comparable	Lower in females	Lower in females	–	Slightly lower in females
Peak onset of disease	Third and fourth decade	Third and fourth decade	–	Third and fourth decade	–

was 2.5:1. It was reported in this study that females had lower mean age of onset compared to males. In a latter study by Bedi (1995) which included larger sample size (530), and he reported 2.8% prevalence of psoriasis among dermatology outpatients while male to female ratio continued to be the same. Kaur et al. (1986), Inderjeet Kaur et al. (1997) also reported the prevalence of this disease 1.4 and 2.3 with male and female sex ratio 2.3:1 and 2.03:1 in 1986 and 1997 respectively.

4.3 Genetics and familial incidence

Many HLA antigens and complement components have been linked to *psoriasis vulgaris*, however there is little information concerning Indians in the majority of published studies. In a study of 67 psoriasis patients from Western India, Chablani et al. (1992) discovered a connection with the A1, B17, and Cw6 antigens but not the B13 antigen. In South India, HLA Bw57 and DR7 have been linked to *psoriasis vulgaris*, according to Pitchappan et al. (1989). HLA Bw57 has found to be increased in Sjögren's patients and it was found that females can develop the disease at early onset than males. The etiopathogenesis of psoriasis is significantly influenced by genetic susceptibility, and familial clustering of the cases has been seen. In 36% of their cases, Farber and Nall (1974) reported familial incidence. Compared to adult-onset psoriasis, juvenile psoriasis has a higher familial occurrence. Studies from India show a decreased disease related familial occurrence. In 14% of their patients, Bedi (1977) documented a positive family history of psoriasis. While only 2% of the patients in Kaur et al. (1986) study reported having a family history. In 84% of the cases, first-degree relatives were impacted, while second-degree relatives were in 12% of the cases. Only a small number of research have documented patients' family history of psoriasis, so precise statistical information on familial occurrence is not yet available.

4.4 Causes

Researchers still don't know the precise cause of psoriasis, which is still a mystery. However, a variety of components, including genetic predisposition and environmental circumstances, are considered to be involved. White blood cells called T cells assault healthy, normal cells in the body, leading to uncontrolled inflammation, which is thought to be a major factor in the development of psoriasis**.** While studies to determine the true origin of psoriasis are underway, it is thought that a weakened immune system, where T cells that fight infection in human bodies erroneously assault healthy cells, may be the problem. The history of the family is also important. Psoriasis is more frequent in the patients whose parents are also victims of this disease. Additionally, those who have bacterial or viral diseases like HIV are more vulnerable to the illness. Other factors that are thought to be contributing to the issue include stress, alcohol use, and obesity. Anything

that has an effect on the human immune system qualifies as a risk factor for psoriasis. The psoriasis is triggered due to the following reasons.

1. Skin Injury: Medications such as Lithium, blood pressure medications can trigger psoriasis. Some antimalarial medications can also cause or worsen psoriasis.
2. Infections: Bronchitis, tonsillitis symptoms, flu, streptococcal infections can set off psoriasis.
3. HIV: Infections like HIV can set off extreme cases of psoriasis, especially in the beginning.
4. Weight: Obese people are at a higher risk of psoriasis and
5. Alcohol: Excessive intake of alcohol can worsen psoriasis.

4.5 Diagnosis

The diagnosis includes both the physical examination as well as laboratory based tests. During physical exam it is usually easy to diagnose psoriasis, especially if you have plaques on areas such as on Ears, Scalp, Knees, Elbows, Belly button and nails The Lab tests include to do a biopsy (remove a small piece of skin and test it to make sure you don't have a skin infection). There's no other test to confirm or rule out psoriasis.

4.6 Prevention

A chronic autoimmune disorder that affects the skin is psoriasis. Although there is no known treatment for the condition, self-care techniques, home remedies, and treatments can help to avoid or lessen flare-ups (Rahman et al., 2012). A crucial approach for those with psoriasis is moisturizing. This is due to the fact that dryness can create flare-ups and severe skin scaling that results in skin cracking and bleeding. Maintain proper scalp hydration, employing a humidifier and vitamin D sufficiency is used for prevention of this chronic autoimmune disorder. It's crucial to keep the scalp hydrated while psoriasis is present. The National Psoriasis Foundation says salicylic acid and tar shampoos can be beneficial. Keeping the air moist at home involves using a humidifier. This could lessen the signs of psoriasis and hydrate the skin. In the winter, a humidifier could be very beneficial. According to some sources, vitamin D insufficiency is prevalent in psoriasis sufferers, especially during the winter. Psoriasis can also be triggered due to the elevated stress (Rahman et al., 2012).

4.7 Treatment

Commonly used therapies for treatment of psoriasis include the steroids creams and skin moisturizing products like Carbon tar (a common treatment for scalp psoriasis available in lotions, creams, foams, shampoos, and bath solutions), a powerful brand of vitamin D-based lotion or ointmentis usually recommended by the dermatologist. Among the therapies for moderate to severe psoriasis are; light treatment where skin will be exposed

to ultraviolet radiation to slow the formation of skin cells. Psoralen medication and a specific type of ultraviolet light is used in the PUVA (Psoralen with UVA radiation) treatment and Methotrexate can also be used (Ling et al., 2016). This medication should only be used in severe cases because it can lead to lung, liver, and bone marrow disorders. Lab tests, probably a chest X-ray, and perhaps a liver biopsy will be required. Another one includes; Retinoids which include vitamin A-related pills, creams, foams, lotions, and gels belong to a class of medications. Cyclosporine is another drug used in serious conditions that do not respond to other treatments may be treated with this immune system suppressing medication. Because it raises blood pressure and can harm the kidneys, your doctor will closely monitor your health while you take it. Rheumatoid arthritis and psoriasis are both conditions that are treated with cyclosporine A, which is made by fermenting the fungus *Trichoderma polysporum* (now known as *Tolypocladium inflatum*) (Kuhn et al., 2011). Green tea, *Camellia sinensis*, has been extensively researched for its advantageous health effects. Epigallocatechin-3-gallate (EGCG), one of the most effective chemicals that has been linked to a number of these positive health effects, has been found to be rather safe for both people and animals. Epigallocatechin-3-gallate (EGCG) is a strong antioxidant and a JAK inhibitor that has been shown to be useful in treating a variety of disorders, including autoimmune diseases. Another way out is to use biological therapies. These function by inhibiting the area of the immune system that the body's hyperactive psoriatic immune system. There are several biologic drugs available, including adalimumab (Humira), brodalumab (Siliq), certolizumabpegol (Cimzia), etanercept (Enbrel), guselkumab (Tremfya), infliximab (Remicade), ixekizumab (Taltz), risankizumab-rzaa (SKYRI (Stelara). Deucravacitinib (Sotyktu) and apremilast (Otezla) are two new types of drugs for chronic inflammatory conditions like psoriasis and psoriatic arthritis. These medicines stops a certain enzyme from doing its job, slowing down other inflammatory processes in the process. Tapinar of (Vtama) which is a topical cream can be applied to any part of the body once a day. There is some evidence that three herbs or herbal treatments — *Mahonia aquifolium*, *Indigo naturalis,* and *Aloe vera* - can improve psoriasis symptoms by reducing inflammation or skin cell growth. The effectiveness of treatment will depend on many factors, such as the severity of the condition or the time of diagnosis (Farahnik et al., 2017). As *Aloe vera*, *Trigonella arabica*, *Catharanthus roseus* and *Anthemis cotula* were the most frequently used medicinal plants by patients with psoriasis who participated in this study based on Ethnopharmacological survey of medicinal plants used by patients with psoriasis in the West Bank of Palestine (Shawahna & Jaradat, 2017). The clinical effects of topical *Hypericum perforatum* in plaque-type psoriasis were studied by Mansouri et al. (2017). According to the findings, all variables, including erythema, scaling, and thickness, were substantially reduced in places where the formulated ointment was applied. *Salvia miltiorrhiza* may also have some antipsoriatic capabilities. Previous studies in vitro on HaCaT cells stimulated IL-1, IL-17, IL-22,

and oncostatin M and in vivo studies on mouse stimulated IMQ showed that extracts from the root of *Salvia miltiorrhiza* could reduce inflammation by scavenging free radicals and inhibiting Akt and ERK1/2 phosphorylation (Baek et al., 2012).

5. Conclusion and future perspectives

With the advent of research more understanding about the nature, causes and mechanisms dealing with autoimmune diseases have emerged which has nearly shifted the focus toward its management and control. The successful introduction of medicinal plants has somehow reduced the menace of autoimmunity but still significant impact of these diseases needs a more robust strategy. There is an urgent need of harmonized research and technological approach in order to efficiently use the medicinal plants for treating the above mentioned diseases.

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CHAPTER 11

Medicinal plants with immunomodulatory properties

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1. Introduction

1.1 Immune system & immunity

Immune system is the inbuilt defense system of body which identifies, fights back and resists a number of pathogenic and potentially detrimental microbes, which in turn safeguards the body against a multitude of diseases and hence supporting the vitality of an organism. Immunity of an organism can be triggered by many factors like exposure to infection, immunization and various kinds of stimuli (Baxter, 2007; Jantan et al., 2015). However, the immune response, irrespective of the causative stimulus, is not indiscriminate in a healthy organism, rather it is collective and very well orchestrated response of specific cells & proteins against specific intruders known as antigens (Jantan et al., 2015). The immune system of an organism differentiates between self and non-self cells by means of what is called as Major Histocompatibility complex (MHC class I). To further simplify the notion, these complexes are the "Self tags" which every nucleated cell in human body possess to identify them as self. Moreover, the immune system isn't confined to any particular part of the body. Instead, the immune system, which is a collaboration of cells and proteins, is dispersed throughout the body to provide rapid and precise response to infections. There are two types of immune barriers in a human body, which provide very well layered immune protection against foreign bodies known as antigens: 1. Innate immunity, also known as natural or genetic immunity, is what an organism is born with inherently. These include physical (skin, tears, mucous, blood clotting), chemical (complement system, interferons & interleukin-1) and cellular defenses (phagocytes, natural killer cells & mast cells). 2. The adaptive or acquired immunity is what an organism acquires or adapts during the course of life upon exposure to various antigens through infection or immunization. It consists of overlapped response of cell-mediated immune system executed by T-cells and humoral response brought about by B-cells and antibodies. The immune cells originate from stem cells in bone marrow known as Hematopoietic stem cells and holds pinnacle importance in immune system of an organism. Immune stem cells, produced in the bone marrow, mature along different pathways to give rise to various types of immune cells. The immune system consists of two

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mechanism-wise different but overlapping pathways: 1. The antibody mediated defense system (Humoral Immunity) brought about by antibody molecules that are secreted by plasma cells. 2. The Cell-mediated immunity (Cellular Immunity) executed by thymus derived T-cells and also by B-cells. Fig. 11.1 illustrates the development, maturation and differentiation of different immune cells.

2. Immunomodulation

In a healthy organism, under ideal conditions, the immune system maintains homeostasis within the body. However, the function and the precise efficacy of the immune system is greatly influenced by a variety of endogenous and exogenous factors leading to either immunosuppression or immunostimulation. The molecules, irrespective of their origin (biological or synthetic), which have the potential to modulate, suppress or stimulate the immune response of an organism are known as Immunomodulators and the process is known as Immunomodulation (Jantan et al., 2015; Puri et al., 1994). Based on the impact on immune system, the immunomodulators are categorized into three categories; 1. Immunoadjuvants. 2. Immunostimulants and 3. Immunosuppressants.

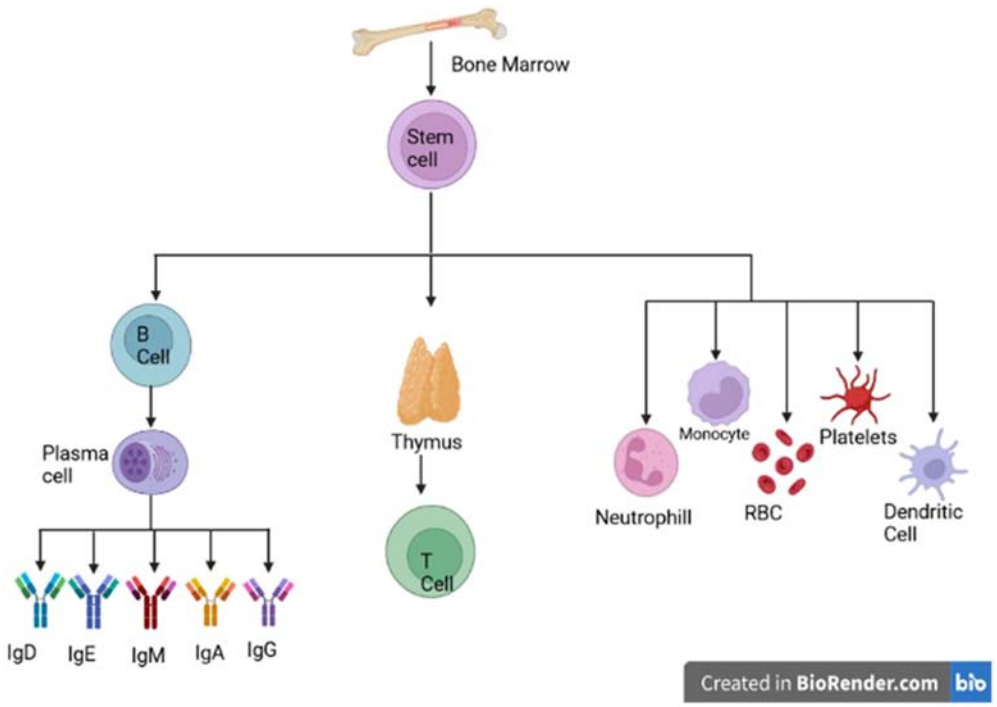

Fig. 11.1 Immune system cell illustration of development, maturation and differentiation of immune cells.

Immunoadjuvants are the agents which enhance the efficacy of immunization upon vaccination. For instance, Sorbitan trioleate adjuvant (MF59), an adjuvant of Novartis influenza vaccines approved in 1997. Molecules which stimulate or induce the components of immune system are termed as Immunostimulants. Examples include β-glucans, chitin, lactoferrin, vitamin B (Sakai, 1999). In contrast to that, Immunosuppressants are the agents which suppress or inhibit the immune response and are used in case of organ transplantation. Further, Immunosuppressants find their use in the treatment of Immunopathology, autoimmune diseases & hypersensitivity reactions (Jantan et al., 2015). Many developments, with regard to the genesis of synthetic immunomodulators, have been done such as monoclonal antibodies. However, given the risk and adverse effects involved, agents of immunomodulation with surplus safety are still in need. Keeping in consideration the chemical adversity of synthetic modulators, naturally derived immunomodulators have proved to be an excellent alternative in clinically relevant therapeutic regimes.

2.1 Immunomodulation via plant based single formulations and combinatorial therapies

Majority of research nowadays is focused on single compound formulations to attain high selectivity for cellular targets and diseases along with low cellular toxicity. Therefore, the drug development from various conventional and alternate medicine systems is gaining popularity. Among the conventional or alternate system of medicine, plants have always been a natural choice due to their high diversity and availability of untapped plethora of phytochemicals produced by them. Whether it is antimicrobial potentiating effects of *Gallic acid* & *Tannic acid* or the antimalarial effects of the famous *Artemisinin* (Sadeer & Mahomoodally, 2021; Weathers et al., 2014), plants have always proved to be the best option when it comes to drug development in complementary medicine.

2.2 Indian traditional medicine and the practice of Ayurveda

India beholds one of the world's oldest medical systems known as "Ayurveda". Evolved almost 3000 years ago in India, Ayurved or Ayurveda is readily considered as the complementary Alternative Medicine (Hajar, 2013). As correctly commented by a French physician, Jean Filliozat (1906–82) that "*Indian Medicine has played in Asia the same role as Greek Medicine in the west, for it has spread in Indo-China, Indonesia, Tibet, Central Asia, and as far as Japan, exactly as Greek Medicine has done in Europe and the Arab countries …*". The different healing and health care measures mentioned in Ayurveda, to be followed by an individual, are put in together under the domain of "Rasayana". The ayurvedic system of healing and treatment address the concept of immunomodulation by the term Rasayana. The overall resistance of body against pathogenic infections achieved by the use of herbs has always been a driving force of Ayurveda (Saboo, 2021).

2.2.1 Concept of Rasayana

Rasayana is a therapeutic practice in Ayurveda which enhances the longevity, slows down the process of aging, boosts memory health and provides resistance and immunity against infections.

2.2.1.1 Classification

On the basis of specificity of treatment and the disease or disorder targeted, Rasayana is divided into the following four main categories, as summarized in Fig. 11.2.

1. **Kamyarasayana**: This sub-domain of Rasayana deals with the drugs which improves the health and vigor of a healthy individual. *Cyavanprasa* is commonly used for this purpose.
2. **NaimittikaRasayana**: These drugs are used to rejuvenate the strength of a diseased person. The drugs in this system are used as adjuvant to a specific medical treatment so as to potentiate the drug and fasten the recovery process.
3. **MedhyaRasayana**: The drugs of this class play vital role in rejuvenating mental health. Sankhapuspi, Brahmi, Vaca etc. belongs to this group.
4. **AcaraRasayana**: This deals with the practices involving habits of healthy life style. Healthy eating habits, meditation, restraining from narcotics and alcoholic beverages etc.
    - *Adapted with modification from National Health Portal, Govt of India, 2015* (https://www.nhp.gov.in/rasayana_mtl).

2.2.1.2 Immunomodulation by Rasayana herbs

The herbs used in Rasayana, as discussed earlier, potentiates the overall immune strength of the body and safeguards it from pathogenic infections. Moreover, some of the Rasayana medications are prescribed to the somatic degenerative disease condition for immunomodulation and adaptogenic effects. Ashvagandha (*Withania somnifera*), Guduchi (*Tiansporra cordifolia*), Amla (*Emblica officinalis*) and Haritaki (*Terminalia chebula*) are few of the plants used for immunomodulation and adaptogenic purposes. Few other Rasayana plants with immunomodulating properties and used in psychomodulation are Shankhapushpi (*Convolvulus plenricaulis*), Mulethi (*Glycirrhiza glabra*), Guduchi (*Tinospora cordifolia*) and Mandookparni (*Bacopa Monieri*). Apart from the above-mentioned disorders, the Rayasana herbs find a plethora of applications. To name a few, Kutki (*Picrorhiza kurroa*) is used to cure liver disorders, Vijaysara (*Pterocarpus marsupium*) to cure diabetes mellitus, Vidang (*Abies webiana*) to treat Helminthic induced gastrointestinal problems, Bhallatak (*Semecarpur anacardium*) as a remedy against piles and autoimmune disorders, Bakuchi (*Psorylia corylifolia*) as a medication against Leucoderma, Shires, (*Albizzia lebek*) to alleviate allergic conditions. Haldi (*Curcuma longa*) is extensively used to treat urinary, allergic and septic problems

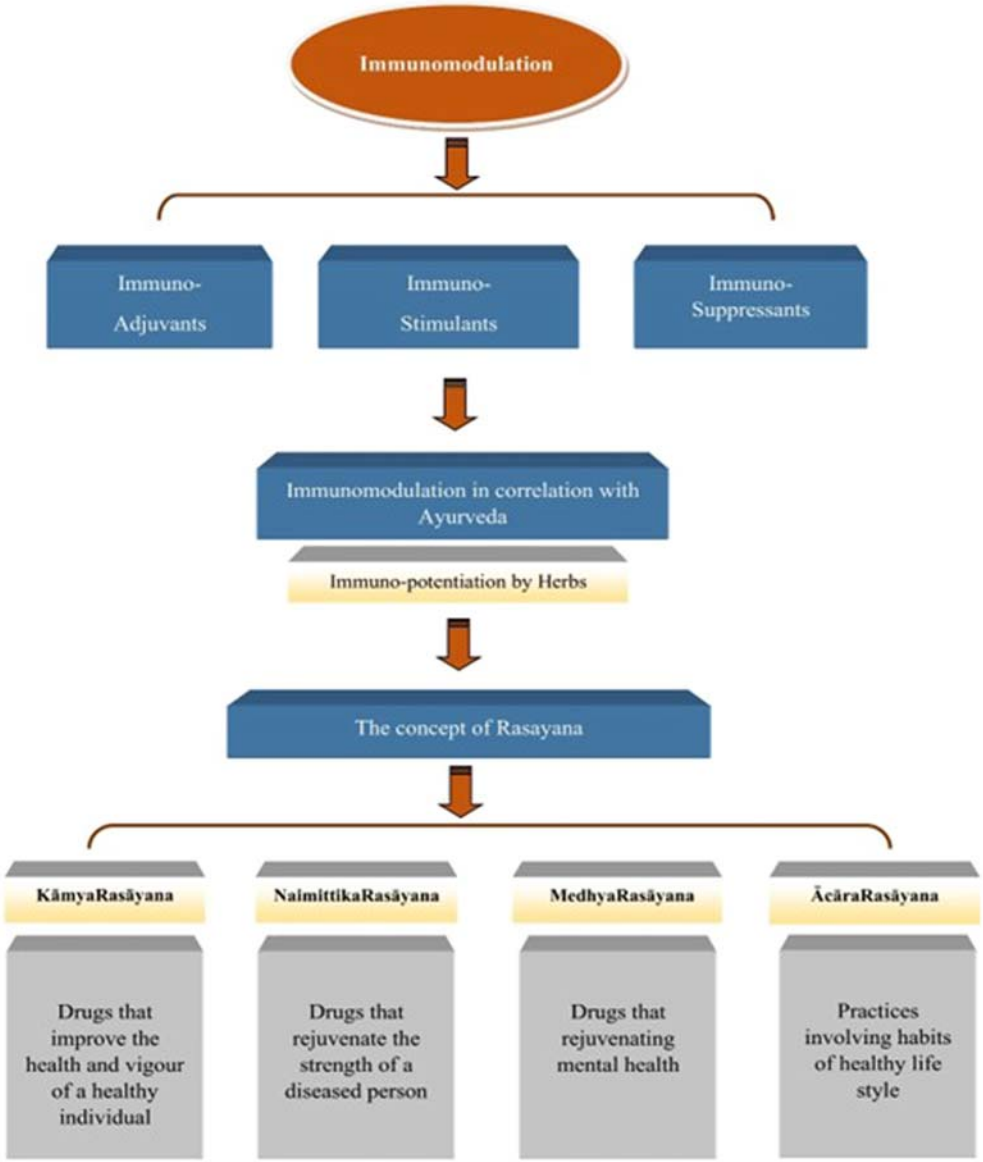

Fig. 11.2 Summary and categorization of Rasayana..

while Neem (*Melia azadiracta*) and Khadir (*Acacia catechu*) to treat skin infections. Apart from these, there are a number of plant species which have been extensively used in traditional medicine system as curatives against a variety of human disorders and are very well documented as immunomodulatory agents, as summarized in Table 11.1.

Table 11.1 Summary of selected medicinal plants used as curatives and immunomodulatory agents in complementary and alternate medicine.

S. no.	Plant name	Family	Vernacular name	Plant part used	Biological activity	References
1	*Abutilon indicum*	Malvaceae	Atibalaa	Whole plant	Diuretic, antibacterial	Dashputre and Naikwade (2010)
2	*Acacia catechu*	Leguminose	Khadira	Leaf	Hypoglycaemic, astringent	Ismail and Asad (2009); Khare (2007); Nadkarni and Nadkarni (2005)
3	*Acanthopanax sessiliflorus*	Araliaceae	Prickly spine	Shoots and roots	Lympho-proliferative activity	Jeong et al. (2006)
4	*Achillea millefolium*	Compositae	Yarrow	Leaves	Anti-inflammatory, anti-spasmodic, anti-pyretic and diuretic	Sharififar et al. (2009)
5	*Actinidia macrosperma*	Actinidiaceae	Actinidia	Fruits	Antileprotic	Lu et al. (2007)
6	*Allium hirtifolium*	Alliaceae	Persian shallot	Whole herb	Anti-rheumatic, anti-inflammatory	Jafarian et al. (2003)
7	*Aloe barbadensis*	Liliaceae	Kumaari	Leaf gel	Purgative, emmenagogue, emollient, anti-inflammatory.	Cooper and Turcasso (1999)
8	*Alternanthera tenella*	Amaranthaceae	Snowball	Whole herb	Anti-tumor, anti-inflammatory	Guerra et al. (2007)
9	*Andrographis paniculata*	Acanthaceae	Kaalmegha	Leaves	Hepatoprotective, anti-spasmodic, purifier and febrifuge	Khare (2007); Shrivastava et al. (2011)
10	*Apium graveolens*	Apiaceae	Celery seeds	Leaves and seeds	Anti-inflammatory	Cherng et al. (2008)
11	*Artemisia annua*	Compositae	Tethwen, damanaka	Whole herb	Anti-malarial, immunosuppressive	Noori et al. (2004)

12	*Asparagus racemosus*	Liliaceae	Shatavaari	Roots	Ulcer healing agent, nerve tonic, anti-gout	Bopana and Saxena (2017); Nadkarni and Nadkarni (2005)
13	*Bauhinia variegata*	Caesalpiniaceae	Kaanchana	Roots, bark and buds	Anti-fungal and astringent	Ghaisas et al. (2009)
14	*Bidens pilosa*	Asteraceae	Begger-ticks, kataka	Flowers and leaves	Anti-inflammatory, immunosuppressive, anti-bacterial and anti-malarial	Chang et al. (2007)
15	*Boerhaavia diffusa*	Nyctaginaceae	Punarnava	Whole herb	Immunostimulatory	Mungantiwar et al. (1999)
16	*Boswellia* spp.	Burseraceae	Shallaki	Gum resin	Hypoglycemic	Mikhaeil et al. (2003)
17	*Byrsonima crassa*	Malpighiaceae	Byrsonima	Leaves	Anti-microbial and anti-oxidant	Bonacorsi et al. (2009)
18	*Calendula officinalis*	Asteraceae	Genda, garden marigold	Flowers	Anti-tumor, anti-viral and Anti-HIV activity	Medina et al. (2006)
19	*Camellia sinensis*	Theaceae	Cha syamaparni	Leaves	Anti-cancer, anti-cataract, lipid lowering, hepatoprotective and anti-oxidant activity	Bhatt et al. (2010)
20	*Cannabis sativa*	Cannabaceae	Bhanga, common hemp	Leaves	Immunomodulatory	Killestein et al. (2003)
21	*Centella asiatica*	Umbelliferae	Brahmi	Whole herb	Immunomodulatory	Mali and Hatapakki (2008)
22	*Chlorophytum borivilianum*	Liliaceae	Safed musli	Roots	Anti-fungal	Thakur et al. (2007)
23	*Cissampelos pareira*	Menispermaceae	Paatha	Roots	Antipyretic, analgesic and anti-lithic activity	Bafna and Mishra (2010)
24	*Cistanche deserticola*	Orobanchaceae	Cistanche	Whole herb	Immunomodulatory, mitogenic and comedogenic activity.	Ebringerová et al. (2002)

Continued

Table 11.1 Summary of selected medicinal plants used as curatives and immunomodulatory agents in complementary and alternate medicine.—cont'd

S. no.	Plant name	Family	Vernacular name	Plant part used	Biological activity	References
25	*Citrus natsudaidai*	Rutaceae	Japanese summer grape fruit	Fruits	Antioxidant	Tanaka et al. (1999)
26	*Cleome gynandra*	Capparidaceae	Tilaparni	Leaves, seeds and roots	Anti-inflammatory	Gaur et al. (2009)
27	*Cordia superba and C. rufescens*	Boraginaceae	Shleshmataka	Leaves, fruit and bark	Anti-inflammatory and anti-microbial	Oliveira Costa et al. (2008)
28	*Couroupita guianensis*	Lecythidaceae	Nagalinga	Fruits and flowers	Anti-fungal	Pradhan et al. (2009)
29	*Crinum latifolium*	Amaryllidaceae	Sudarshana, sukhdarshan	Whole herb	Immunomodulator	Zvetkova et al. (2001)
30	*Echinacea angustifolia*	Asteraceae	Narrow-leaved purple coneflower	Flowers	Anti-flu, immunomodulator	Senchina et al. (2005)
31	*Eclipta alba*	Compositae	Bring raj	Leaves	Anti-cancer, anti-leprotic, analgesic, anti-oxidant and anti-myotoxic	Jayathirtha and Mishra (2004)
32	*Euphorbia hirta*	Euphorbiaceae	Asthma weed, hairy spurge, snake weed	Whole herb	Anti-inflammatory, sedative and anxiolytic	Patil et al. (2009)
33	*Evolvulus alsinoides*	Convolvulaceae	Shankh pushpi	Whole herb	Brain tonic	Ganju et al. (2003)
34	Genus *Ardisia*	Myrsinaceae	Marlberry	Shrub, branches and leaves	Anti-metastatic and Anti-HIV property	Kobayashi and De Mejía (2005)
35	Genus *Aristolochia*	Aristolochiaceae	Pipevine	Leaves	Anti-angiogenic, used in treatment of prostate cancer	Wang et al. (2010)

36	*Gymnema sylvestre*	Asclepiadaceae	Gurmaar	Leaves	Anti-diabetic, diuretic and anti-bilious	Malik et al. (2009)
37	*Haussknechtia elymatica*	Apioideae	Haussknechtia	Whole herb	Immunomodulator	Amirghofran et al. (2007)
38	*Heracleum persicum*	Apiaceae	Golpar	Shrub	Anti-microbial	Sharififar et al. (2009)
39	*Hibiscus rosa sinensis*	Malvaceae	Japaa	Flowers	Anti-diarrheal and anti-inflammatory	Gaur et al. (2009)
40	*Hyptis suaveolens*	Lamiaceae	Tumbaaka	Leaves and flowers	Carminative and anti-spasmodic	Jain et al. (2005)
41	*Lagenaria siceraria*	Cucurbitaceae	Katu-tumbi	Leaves and fruits	Purgative and emetic	Deshpande et al. (2008)
42	*Larrea divaricata*	Zygophyllaceae	Chaparral	Whole herb	Anti-inflammatory	Davicino et al. (2007)
43	*Lycium barbarum*	Solanaceae	India lyceum, kasmale	Fruits and roots	Antioxidant	Gan et al. (2003)
44	*Matricaria chamomilla*	Asteraceae	Babuna	Flowers	Immunomodulator	de Souza Reis et al. (2008)
45	*Mollugo verticillata*	Molluginaceae	Indian chickweed, green carpetweed	Whole herb	Immunomodulator	Ferreira et al. (2003)
46	*Moringa oleifera*	Moringaceae	Mungna, saijna	Leaves	Antioxidant	Gupta et al. (2010)
47	*Morus alba*	Moraceae	Brahmdaru	Fruits, leaves and bark	Decongestive, hypocholesterolaemic, diuretic	Bharani et al. (2010)
48	*Murraya koenigii*	Rutaceae	Surabi-nimba	Leaves	Anti-fungal and insecticidal	Khare (2007); Shah et al. (2008)
49	*Nyctanthes arbo-tristis*	Oleaceae	Paarijaata	Leaves and seeds	Anti-inflammatory and anti-spasmodic	Kannan et al. (2007)
50	*Ocimum sanctum*	Labiate	Tulsi	Entire shrub	Diaphoretic, anti-asthmatic, hepatoprotective	Nadkarni and Nadkarni (2005); Vaghasiya et al. (2010)

Continued

Table 11.1 Summary of selected medicinal plants used as curatives and immunomodulatory agents in complementary and alternate medicine.—cont'd

S. no.	Plant name	Family	Vernacular name	Plant part used	Biological activity	References
51	*Panax ginseng*	Araliaceae	Ninjin	Fruits and roots	Adaptogenic properties	Kang and Min (2012); Khare (2007)
52	*Picrorhiza scrophulariiflora*	Scrophulariaceae	Kutki	Roots	Antioxidant	Smit (2000)
53	*Piper longum*	Piperaceae	Pipala, indian long pepper	Fruits	Antioxidant	Sunila and Kuttan (2004)
54	*Randia dumetorum*	Rubiaceae	Madana	Fruits	Anti-arthritic	Satpute et al. (2009)
55	*Rhodiola imbricata*	Crassulaceae	Rose root	Rhizomes	Immuno stimulating properties	Mishra et al. (2008)
56	*Salicornia herbacea*	Chenopodiaceae	Common glasswort	Whole herb	Immunomodulator	Im et al. (2006)
57	*Silybum marianum*	Asteraceae	Dooshpatra, milk thistle	Flowers	Antioxidant	Meeran et al. (2006)
58	*Terminalia arjuna*	Combretaceae	Arjuna	Leaves and bark	Cardio tonic, diuretic and anti-hypertensive	Halder et al. (2009)
59	*Thuja occidentalis*	Arborvitae	White cedar	Leaves	Immunomodulator	Gohla et al. (1992)
60	*Tinospora cordifolia*	Menispermaceae	Guduchii	Whole herb	Hypoglycaemic and anti-pyretic	Nadkarni and Nadkarni (2005); Sinha et al. (2004)
61	*Urena lobata*	Malvaceae	Naagabala	Roots and flowers	Diuretic, emollient and anti-spasmodic	Rinku et al. (2009)
62	*Viscum album*	Loranthaceae	Common mistletoe	Leaves	Anti-tumor effect	Elluru et al. (2007)

3. Immunomodulation by plants

3.1 Regulation of immune response- cellular interaction

Collaborative interactions between the components of immune system leads to well organized and orchestrated immune response to prevent any health condition. The two different yet overlapping mechanisms of immune response of Humoral and Cellular immune system of an organism are intensive and intimate (Amit & Govind, 2022). In case of an infectious coup in the body, the T-lymphocytes engage a juxtracrine interaction with macrophages for immune activation (Chang et al., 2008). Macrophages act as Antigen Presenting Cells (APCs) to T-lymphocytes and in the process of interaction, many other cells are involved, like activated monocytes and macrophages, which produces monokines, thus enabling interactions with lymphocytes. Moreover, the mediator cells (mast cells, eosinophils, basophils and platelets) release soluble mediators like chemotactic factors, platelet activating factors, prostaglandins, leukotrienes and heparin, which brings about the inflammatory response post an immune reaction (Amit & Govind, 2022; Brown, 1991; Detmers & Wright, 1988). Besides the collaborative responses, the macrophages and lymphocytes also pose their individual effects. The cell-to-cell interaction mediators known as cytokines (monokines & lymphokines) provoke specific activities resulting in lymphocyte proliferation. The lymphokines hence produced by the T-lymphocytes (IL-2), in turn activate macrophages, which eventually leads to enhanced phagocytosis. The Lymphokines designated as IL-5 enhance the chemotactic effects of Basophils, Neutrophils and Eosinophils at the area of inflammation (Amit & Govind, 2022). The mentioned mechanism of immune system, although incomplete, is a snapshot of the functional interactions between humoral & cellular immunity component (Colegate & Molyneux, 1993, p. 279–317). Several plants possess immunomodulatory properties as discussed below. *Ganoderma lucidum, Glycyrrhiza uralensis, and S. flavescens* have inhibitory effecton airway hyper-responsiveness modulating ovalbumin level of IgE and associated cytokines IL-5, IL-4, and IL-13 (Halwani et al., 2016). The ethanolic extracts of *Fiscus carica* have reportedly posed stimulatory effect on humoral as well as cell mediated immune response (Patil et al., 2010). *Chlorophytum borivilianum* has been reported to complement non-specific immunity in addition to humoral as well as cell-mediated immunity. It has been found to modulate immunity in case of an infection condition and revitalize immunological strength in normal circumstances too (Thakur et al., 2007). *Picrorhiza kurroa,* a well-studied and researched plant of Indian Himalayas, modulates humoral immunity by boosting the antibody production, mediates release of cytokines in case of hypersensitivity reactions and host response toward the mediators in the target organ (Hussain et al., 2013).

3.2 Immunomodulation in cardiovascular disorders

The heart and the immune system are highly integrated systems, in dialog through cytokines, hormones and neurotransmitters. Their balance can be altered by numerous physical or psychological stressors leading to the onset of inflammation, endothelial dysfunction and tissue damage (Dal & Carlo, 2019). Recent evidence has shown that immuno-inflammatory mobilization has a profound role in cardiovascular disorders, thereby venting out novel and unconventional choices of treatment. Besides, after it was demonstrated that atherosclerosis is primarily a result of chronic inflammatory disorder of the arterial wall, research suggest that any possible dysregulation of the immune system and inflammatory cascades might be the pioneering cause of number of cardiovascular diseases including congestive heart failure, pericardial disorders, heart arrhythmia and cardiomyopathies (Lazzerini et al., 2019; Libby et al., 2019; Swirski & Nahrendorf, 2018). The production of increased levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS) have been observed in case of localized and systemic inflammatory responses, caused due to any dysregulation in physiological functions (Mangge, 2014). The increased ROS production reportedly decrease nitric oxide supply and availability thus causing vasoconstriction which eventually leads to arterial hypertension. In addition, ROS also has a negative impact on myocardial calcium handling resulting in arrhythmia and cardiac remodeling via induction of hypertrophic signaling and apoptosis. The increased levels of ROS is also associated with atherosclerotic plaque formation (Senoner & Dichtl, 2019). Patients suffering from immuno-inflammatory diseases often have scarce levels of antioxidants more likely due to hyped up demands in situation of high ROS production by immune effector cells like macrophages (Mangge, 2014). This is where plants and plant-based formulations containing high levels of antioxidants find application. The plant phytochemicals act as natural antioxidants which clear off the ROS produced in case of an emergency and surged immune response, thereby modulating the immune system and the effects of an immuno-inflammatory response. Cardamonin, a chalcoloid (a class of flavonoid) found in black cardamom has been demonstrated to relax fluoride, phenylphrine and phorbol ester induced vascular contractions (Je & Jeong, 2016).

The following sub-section discusses about some of the plants which act as immunomodulators in cardiovascular diseases.

3.2.1 Citrus medica

The leaves and fruits of *Citrus medica* have medicinal value in traditional practice as a treatment for heart palpitation and weakness (Sina, 1984). The most abundant bioactive compound of the plant is known as Limonene, which has been found to bind to adenosine A2A receptors (a G-protein-coupled receptor that plays crucial role in regulating coronary blood flow and myocardial oxygen supply) resulting in its activation. The activation causes vasodilation in coronary artery and aorta, activates protein kinase A

signaling cascade, thereby inhibiting platelet aggregation and reduces the inflammatory response during ischemia-reperfusion (Park et al., 2011; Patel et al., 2020; Sobhani et al., 2017).

3.2.2 *Crocus sativus*

The aqueous extract of *Crocus sativus* (saffron) along with the its main constituents, Safranal and Crocetin (a glycosylated carotenoid) has been found to have profound effect on the reduction of mean arterial blood pressure (MABP) in a dose dependent manner, as tested in hypertensive rat models (Imenshahidi et al., 2010). Saffron and its constituents have been found to modulate cardio-protective health by strengthening antioxidant defense system (Sachdeva et al., 2012). Crocetin was found to attenuate atherosclerosis in hyperlipidemic rats through inhibition of low-density cholesterol oxidation (Zheng et al., 2006). In an older study conducted by Verma & Bordia, human models were given regular doses of saffron (50 mg saffron in 100 mL milk twice daily for 6 weeks) to test the susceptibility of lipoprotein oxidation. The results demonstrated great reduction in lipoprotein oxidation susceptibility during the period of saffron consumption in human models (Verma & Bordia, 1998).

3.2.3 *Amomum subulatum* Roxb.

Amomum subulatum, commonly known as "black cardamom", has been reported to enhance antioxidant enzyme activities and reinstate growth stimulating hormone levels in high fat diet fed rat models (Dhuley, 1999). Cardamonin, belonging to an important class of plant flavonoids known as Chalconoids, has been shown to relax fluoride, phenylephrine and phorbol ester induced vascular contractions. It has been reported to have inhibitory action on fluoride induced surge in phosphorylated myosin phosphatase target subunit 1 (pMYPT1) level and phenylephrine generated surge in mitogen activated protein kinase activity, the enzyme has a profound role in cardiovascular diseases including abnormal smooth muscle contraction and hypertension (Jeong et al., 2006; Liao et al., 2007). Cineole, a monoterpene oxide of black cardamom has been reported to exert antihypertensive effects via vasorelaxation along with the regulation of oxidative stress (Lahlou et al., 2002; Moon et al., 2014).

3.2.4 *Lavandula stoechas* L.

The ethanolic extracts of this plant have displayed antioxidant properties against diabetic rats (Sebai et al., 2013). The bioactive constituents of the plant are the pentacyclic triterpenoids: oleanolic & ursolic acid, which have demonstrated anti-inflammatory, antioxidant and hypolipidemic functions (Somova et al., 2004). A flavone compound known as luteolin has been found to pose positive inotropic effects along with vasodilation, probably via improvement in myocardial perfusion and free radical scavenging (Rump et al., 1994).

3.2.5 *Melissa officinalis* L.

The oleanolic and ursolic acids found in the ethanolic extract of *Melissa officinalis,* commonly known as Lemon balm, has been demonstrated to reduce plasma lipid in mice models (Weidner et al., 2014). Because of its antioxidant properties, the plant might find its use in the inhibition of LDL oxidation and considerable reduction of arterial foam cell formation (Ferreira et al., 2006; Luño et al., 2015). Rosmarinic acid is one of the main constituents of lemon balm and was found to possess various cardiovascular health benefits including cardio protection, prevention of lipoprotein oxidation as well as endothelium dependent vasodilation (Ferreira et al., 2013).

3.3 Immunomodulation in microbial infections/diseases

Microbial diseases have always been a curse to human race since the beginning of civilization. It was until 1910, when Paul Ehrlich discovered Arsphenamine or salvarsan as the first effective treatment for syphilis and African trypanosomiasis. This discovery marked the introduction of first modern antimicrobial agent in the antibiotic market. Moreover, the period from 1940 to 62 served as a golden period in the antibiotic discovery and in fact, most of the antibiotics that are in use nowadays, were discovered in that period. However, over-the-counter availability and ignorant consumption/usage of antimicrobials have yielded a far more dangerous problem of antimicrobial resistance. Recent years have shown an increasing trend toward the use of alternative therapies based on herbal formulations for possible immunomodulation against microbial infections. The popularity of plant-based therapies is because of easy availability, having very less or even no side effects along with being cost effective. The plant-based therapies can exert antimicrobial activity in the form of single formulations or it can have host potentiating activity against the infection. The host potentiating activity is what could be called as immunomodulation against microbial infections. Few plants and their bioactive constituents have been evaluated for their antimicrobial activities. For example, the bioactive compound of Berberis species, "Berberine" has demonstrated antimicrobial activities via DNA intercalation, and disruption of cell division machinery (Iwasa et al., 2001). Similarly, *Thymus vulgaris, Scutellaria baicalensis* and *Scutellaria lateriflora* produce a common flavone glycoside compound known as "Baicalein" which has demonstrated antimicrobial potential via inhibition of NorA efflux pump of Methicillin Resistant *Staphylococcus aureus* (MRSA) (Chan et al., 2011; Fujita et al., 2005). The following section discusses about few plants which have immunomodulatory potential against microbial infections.

3.3.1 *Aconitum heterophyllum*

This plant has demonstrated effectiveness against Giardiasis and Diarrhea in traditional medicine (Singh & Chaturvedi, 1981; Sinha et al., 2004). It has been reported to induce phagocytosis along with the inhibition of Sheep Red Blood Cells (SRBC) induced

humoral immune response in mice models (Atal et al., 1986). It has been reported to have up to 50% inhibitory potential against *Sarcina lutea* (Pandya et al., 1990).

3.3.2 Abutilon indicum

Abutilon indicum in powdered form has been reported to stimulate and increase humoral antibody response toward *Salmonella typhimurium* in rabbit models and increase the survival time of rabbits against virulent strains of *Staphylococcus aureus* infection (Dixit et al., 1978).

3.3.3 Asparagus racemosus

Asparagus racemosus demonstrated protective properties in mice against peritoneal sepsis and showed reduction in mortality rates in *Staphylococcus aureus* induced sepsis in mice with neutropenia and hemi splenectomy. It has been reported to have considerable activity against fungal stains like *Candida albicans*. It is very well known to have immunorestorative efficacy against cyclophosphamide induced mylosuppression (Thattet & Dahanukar, 1989).

3.3.4 Cryptolepis sanguinolenta

It has been shown to possess anti-diarrheal activity (Paulo et al., 1994) and the aqueous & ethanolic extracts of the roots have shown activity against 41 strains of *Campylobacter coli* isolated from gastroenteritis patients, 65 strains of *Campylobacter jejuni* and 86 strains of *Vibrio cholera*. Its activity has been claimed to be equal to that of Ampicillin, a penicillin antibiotic (Bamgbose & Noamesi, 1981). The roots also act as broncho dilatory and antihepatitis agent (Cimanga et al., 1991; Gomes & Diniz, 1993, p. 153–163).

3.3.5 Holarrhena antidysenterica

This plant has been used in traditional medicine for a number of diseases like diarrhea, menorrhagia, cholera etc (Jain & Tarafder, 1970). Leaves are used for chronic bronchitis, boils & ulcers. Oil extracted from seeds have shown antifungal activities (Chopra et al., 1933; Deshmukh & Jain, 1981; Kirtikar & Basu, 1918). Moreover, the plant has been in therapeutic utility for amebic dysentery from a long time (Chopra et al., 1927, 1933).

3.3.6 Picrorhiza kurroaroyle

Picrorhiza kurroa is one of the most commonly used medicinal plant in Asian countries especially in the Himalayan belt of India. This plant is used against a wide array of diseases and disorders like inflammation (Jayaweera; Nadkarni, 1954), treatment of bronchial asthma (Rajaram, 1976), infectious hepatitis (Mittal et al., 1978), and arthritic pain of bone joints (Langer, 1981). The root and leaf extracts are known to boost humoral and cell mediated immunity (Atal et al., 1986; Sharma et al., 1988). Its glycoside fraction

is known to supplement bronchodilation effect of isoproterenol adrenaline (Mahajani & Kulkarni, 1977). It is also known to subdue the immunosuppressive effects of betamethasone & cyclophosphamide (Immunosuppressive drugs which act on T and B-lymphocytes, platelet and monocyte activity) (Sharma et al., 1994).

3.4 Immunomodulation in gastrointestinal disorders

3.4.1 *Cnicus benedictus*

This plant is consumed as an amarum (Amara are plants with a predominance of bitter substances and a stimulating action on gastric secretion and gastrointestinal motility) because of predominance of a bitter tasting substance, a sesquiterpene lactone known as Cnicin in addition to trace quantity of essential oil, supporting its use as a stimulant for gastric secretions (Avau et al., 2015).

3.4.2 *Gentiana lutea*

Gentiana lutea contains secoiridoid glycosides such as Amarogentin & Gentiopicroside with characteristic bitter taste. This plant stimulates the digestive tract and enhances the production & release of saliva and gastric acid, enhances blood circulation in the mucosal lining of digestive tract and improves stomachic motility (Kelber et al., 2018).

3.4.3 *Carum carvi*

The fruits of *Carum carvi* contain limonene & carvon as their major constituents, which are known to have spasmolytic and carminative effects and also acts as stimulants for mucous secretion in gastrointestinal tract (Alhaider et al., 2006; Keshavarz et al., 2013).

3.4.4 *Matricaria chamomilla*

The essential oil of this plant contains chamazulene and α-bisabolol as the lead constituent and is involved in relieving inflammation. Moreover, Chamoline has carminative as well as spasmolytic effects making it a suitable therapeutic candidate for acute gastritis. The flowers of the plant contain apigenin-7-glycoside, a flavonoid, which reportedly inhibits peristalsis and is spasmolytic hence used in relieving abdominal spasms, ulcers and dyspepsia (Cemek et al., 2010; Miraj & Alesaeidi, 2016).

3.4.5 *Mentha piperita*

Mentha piperita commonly known as pepper mint contains essential oils and caffeic acid derivatives (Rosamarinic acid), which has predominant spasmolytic activity hence used in dyspeptic conditions (Grigoleit & Grigoleit, 2005).

3.4.6 *Melissa officinalis*

Commonly known as lemon balm, *Melissa officinalis* contains citral, citronellal, linalool, geraniol & β-caryophyllene as its essential oil constituents, besides it contains rosmarinic

acid. It has spasmolytic and carminative effects which supports its application in gastric disorders and spasms (Aubert et al., 2019).

3.4.7 Achillea millefolium

The herb finds its use in gastric hyposecretion, dyspepsia and gastritis. Besides it has antiphlogistic, spasmolytic and carminative properties (Moradi et al., 2014).

3.4.8 Acorus calamus

The roots of *Acorus calamus* yield a bitter tasting essential oil, which contains active substances like asarone, acorin, and tannins. The roots extract is used in hypoacidity, chronic dyspepsia and flatulence. It also has carminative and spasmolytic properties (Gilani et al., 2006).

3.4.9 Artemisia absinthium

Plants of genus *Artemisia* have been extensively studied for their pharmacological and immune modulation activities. The famous example so far has been "Artemisinin", the wonder drug in Artemisinin combination therapies (ACTs) active against drug resistant malaria. Besides, artemisia is popularly used in folklore medicine against Intestinal worn infestation and flatulence. It is used for relieving dyspepsia and hypomotility of intestines (Lee et al., 2020).

3.5 Immunomodulation in respiratory diseases: Emphasis on severe acute respiratory syndrome corona virus-2 (SARS-CoV-2)

SARS-CoV-2 is a member of Corona virus family, which includes viruses that cause a wide array of diseases mostly confined from head to chest ranging from mere cold and cough to more dangerous severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS). The infection from SARS-CoV-2 can be divided into three stages: **1**. Incubation period, which usually remains asymptomatic wherein the detection of viral load may or may not be possible **2**. Symptomatic period is usually accompanied by non-severe symptoms with detectable range of viral load **3**. Severe respiratory symptomatic stage is the ugliest and deadly phase of COVID (Corona Virus Disease) with high scale of viral load (Das, 2022; Wang et al., 2020). As the virus propagates through the body, the impaired cells set off intrinsic inflammation of the respiratory tract mostly lungs by proinflammatory macrophages and white blood cell, especially the granulocytes thereby starting out severe respiratory disorders known as acute respiratory distress syndrome (ARDS) which begin from rapid start of widespread inflammation in lungs (Xu et al., 2020). Many possible medicines were introduced, which were effective in symptom-based treatment but no inclusive medicine was found throughout. In Japan, antiviral drugs such as favipiravir/Avigan were reportedly used for the treatment of

COVID-19. Antimalarial drugs like chloroquine and hydroxychloroquine were used in few countries against COVID-19 (Das, 2022). The Indian Council of Medical Research, India (ICMR) accepted a mix of swine flu, malaria & anti-HIV drugs known by the names Lopinavir & Ritonavir to treat COVID-19 (Jin et al., 2020). Finally, vaccines were developed by a number of national and multinational companies like Pfizer, Johnson & Johnson, Novavax and many more. The mass vaccination was kicked off in early December in 2020. Apart from the vaccines and all the drugs from allopathy, various formulations from alternate medicine mainly from plants sources have been explored and found to be effective in the Immunomodulation to counter COVID-19. The following section mentions about few plants, which have shown immunomodulatory activities in respiratory diseases.

3.5.1 Azadirachta indica

Azadirachta indica, commonly known as "Neem", is used as an antiseptic in majority of households in Indian sub-continent. Nimbin, a bitter compound isolated from neem oil enhances immunity by triggering the phagocytic ability and the antigen presenting capability of macrophages via cytokine stimulation (Thatte & Dhanukar, 1999, p. 141−148). Neem apart from being immunomodulatory, also possesses antiviral properties. Molecular docking studies have shown Desacetylgedunin, a bioactive compound derived from neem to have highest binding affinity for Papain like protease (PLpro) of SARS-CoV-2 (Baildya et al., 2021).

3.5.2 Phyllanthus emblica

Phyllanthus emblica is commonly known as Amla. Its fruits are most commonly consumed as a treatment option against recurrent respiratory infections. The fruit contains high amounts of vitamin C and flavonoid reserves. The main flavonoids being Gallic acid, Ellagic acid and Kaempferol. The fruit extracts modulate immunity by enhancing interleukin-2, natural killer activity & Gamma interferon production (Sai Ram et al., 2002; Sreeramulu & Raghunath, 2010).

3.5.3 Picorrhiza kurroa

Picorrhiza kurroa, commonly known as "Kutki", is an effective immunomodulator used against hepatic and respiratory disorders. Its main phytocompounds include Picroside, kutkin, vanillic acid & apocynin (Das, 2022; Kumar et al., 2016). The bitter bioactive compound Picroside boosts immunity by enhancing phagocytosis and humoral and cell mediated immune response (Sharma et al., 1994).

3.5.4 Ocimum sanctum

Ocimum sanctum, commonly known as "Tulsi", is considered sacred in India. The leaf extract contains ursolic acid and apigenin. The essential oil of the plant contains

1,8-cineole and eugenol as the main constituents. The leaf extract has showed immunomodulatory activity by enhancing IFN-Y, interleukin-4, natural killer cells, T-helper cells and boosts phagocytic activity of macrophages (Mondal et al., 2011). The plant was studied for its antiviral activity against COVID-19 using molecular docking and molecular dynamics simulation approaches and the phytochemicals of the plant have shown to inhibit main protease (M^{pro}) of SARS-CoV-2 (Das, 2022; Shree et al., 2022). Moreover, leaf extracts of the plant were found to be effective against influenza A Virus, H9N2 (Ghoke et al., 2018).

3.5.5 *Withania somnifera*

Withania somnifera, commonly known as "Ashwagandha", contains alkaloids as bioactive principles like anaferine, isopelletierine; steroidal lactones, such as withanolides, wathferins and saponins (Mishra et al., 2000). The isolated compounds sitoindoside IX & sitoindoside X, have shown Immunomodulation via peritoneal macrophage activation involved in phagocytosis (Ghosal et al., 1989).

4. Conclusion and future prospective

The active ingredients produced by plants as secondary metabolites have always been in focus because of their multifocal activities on a host body. As far as the immune system is concerned, any imbalance could result in a catastrophic health condition such as cancer, rheumatoid arthritis, cardiovascular disorders and hypersensitivity reactions. Plants have been studied for their immunomodulatory properties and research have suggested a wide range of medicinal plants and their bioactive compounds to bring about their medicinal effects due to immunomodulatory properties. The anti-inflammatory and antioxidant properties of phytochemicals such as Quercitin, Mangneferin, Gallic acid etc. have made them one of the best choices for Immunomodulation purposes. In addition, phytochemicals have reportedly shown the balancing activity on Th1 & Th2 type cytokines and the associated reactions of inflammation, allergies, infections and transplantation rejection. However, despite having several preclinical and in vitro studies in support of the narrative, sufficient evidences are required to set up a precedent for the immunomodulatory use of plants and plant-based formulations in the prophylaxis of immune related disorders. Moreover, the development of a photochemical into a therapeutic drug needs rigorous evaluation on defined parameters like standardized dosage of the active ingredient, bioavailability, cellular toxicity to the host and the rate of clearance from the body. In addition, inadequate information about mode of action of the formulation raises questions about the efficacy and safety of the phytocompounds. Taking into consideration the necessity of plant-based immunomodulators in prophylactic usage, proper experimentation including in vitro and in vivo trials and evaluation based on pharmacognostic properties is of paramount importance.

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CHAPTER 12

Different types of phytocompounds with immunomodulatory activities

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1. Introduction

Herbal remedies, particularly in underdeveloped countries, continue to be the mainstay of treatment for basic care even though pharmaceutical goods have changed health care for much of the world over the past 100 years (De Pasquale, 1984). The use of herbal therapy differs from the traditional, pharmacological, and organ system approaches seen in Western society in many ways. First of all, unlike our "modern medications," these traditional, botanical forms of medicine typically consisted of blends that were specially created for a patient and largely discovered via trial and error for their ability to control illness (Jones, 1996). A holistic approach to treatment is preferable to one that focuses on treating a single organ system since many traditional medical systems that utilize herbs see illness as a disturbance of the body's homeostasis (Schmidt et al., 2008). Additionally, herbal remedies are not isolated entities because they might encompass the entire plant or any of its parts, such as the roots and bark, which have a range of efficacy and physiological effects (Block & Mead, 2003). Last but not least, the herbal medicine preparations can vary greatly from batch to batch and can include the whole plant, syrups, tinctures (alcohol extracts), decoctions (roots or bark), and cold infusions. Up to one-third of Americans and 80% of the world's population, mostly in Asia and Africa, still utilize herbal remedies (Johnston, 1997). For instance, traditional medicine, which has herbal remedies at its foundation, provides 40% of all healthcare services in China, and it has sections in more than 90% of general hospitals (WHO, 2005). Nevertheless, there are a number of countries where the use of herbs is growing, in particular Australia, Canada, Germany, and the United Kingdom (Wachtel-Galor & Benzie, 2011). In these countries, training in complementary or traditional methods is incorporated into medical education and is more widely acknowledged. The size of the American

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Table 12.1 The table shows total US retail sales of Herbal Supplements (Smith et al., 2020).

Year	Total sales (in billion)	% change
2020	$11.261	17.3
2019	$9.602	8.6
2018	$8.842	9.4
2017	$8.085	8.5
2016	$7.452	7.7
2015	$6.922	7.5
2014	$6.441	6.8
2013	$6.033	7.9
2012	$5.593	5.5
2011	$5.302	4.5
2010	$5.049	3.3
2009	$5.037	5.0
2008	$4.800	1.0
2007	$4.756	4.4
2006	$4.558	4.1
2005	$4.378	2.1
2004	$4.288	3.4
2003	$4.146	−2.3
2002	$4.275	−2.8
2001	$4.361	3.2
2000	$4.225	2.9

From Smith, T., Eckl, V., & Reynolds, C. M. (2020). Herbal supplement sales in US increase by record-breaking 17.3%. In *Sales of immune health, stress relief, and heart health supplements grow during COVID-19 pandemic* (Vol. 131, pp. 52–65).

ethnobotanical market is also not trivial, with current estimates of yearly sales at between $3.2 and $5.1 billion and global estimates of $60 billion (Table 12.1) (Smith et al., 2020).

According to national polls, up to 40% of Americans may occasionally utilize herbal remedies, including saw palmetto, garlic, and ginkgo. Despite the fact that only about 15% of patients seek medical advice; consumers are still drawn to herbal medicines. Patients use herbal medications for a variety of reasons, but the most common is that they believe they are safer and less expensive than prescription drugs, or that the latter have failed to work (Quato et al., 2008). According to studies, some cultures, particularly Asian ones, may believe that herbal remedies are preferable to the medicines that are commonly used in Western medicine (Chan et al., 2003). The African flower is presently being used effectively in the treatment of the wasting associated with HIV sickness for African patients as two main examples in this respect, as part of China's attempts to contain and cure the severe acute respiratory syndrome (SARS) virus in 2013 (Tilburt & Kaptchuk, 2008). Immunomodulating plants and herbs, or those that either stimulate or suppress the immune system, have a long and effective history of treating immune system illnesses, particularly among the Chinese, Indian, and North African populations. The construction of the Egyptian pyramids, which began in 2670 BCE, is perhaps the oldest instance of herbs being used to prevent illness. Large quantities of radishes, garlic, and onions were once fed to slaves as a kind of therapy. The presence of two organosulfur compounds,

allicin and alistatin, in the seeds of garlic, onions, and radish was found in the 1940s. The bacterial strains cocci and Escherichia coli are all suppressed by these three compounds. The top three selling plant medicines worldwide at the moment are *Ginkgo biloba*, *Allium sativum* (garlic), and *Panax ginseng* (Table 12.2) (Babos et al., 2021).

Herbal studies are more common than case reports, and they rank higher on two lists of the most popular herbs. Multiherb species that are not otherwise indicated are only identified as a part of a case involving multiple herbs. These plants also have a 3000-year history of use in traditional Chinese medicines like those mentioned in the Pen Ts'ao King (−221 BCE) (Xutian et al., 2009). Adaptogens, immunostimulants, or both are the common classifications for herbal medications that enhance immune system activity (Block & Mead, 2003). *Ginseng* is one of the herbal supplements known as an adaptogen, which is thought to be able to increase the body's tolerance to stress, including dangers from pathogenic agents (Block & Mead, 2003). Because stress, especially chronic stress, is known to reduce immune system function, these herbs may also help prevent infection (Khansari et al., 1990). Contrary to psychostimulants like coffee, actoprotectors are a subclass of adaptogens that provide advantages to persons in physically demanding or high-stress employment without the negative effects of withdrawal symptoms (Oliynyk & Oh, 2013). They are another class of herbal medications that has the potential to be helpful. Through the stimulation of innate immune pathways, immune-stimulants like *Echinacea* and *Curcumin*, which are botanicals, can increase the clearance of cancer and infectious pathogens Fig. 12.1 (Block & Mead, 2003).

The immune system may not actually be "boosted" by immunomodulators, which instead normalize an overactive immune system or augment a weak immune system

Table 12.2 Shows the ranking on two top selling herb lists as well as the frequency of herb studies in comparison to case reports.

Clinical studies	N Studies	N Case reports	Top selling herb lists rank
Hypericum perforatum St. John's Wort	17	17	0,0
Ginkgo biloba, ginkgo	11	7	17, 21
Panax ginseng, ginseng	6	4 plus 3 NOS	30, 30
Allium sativum, garlic	3	1 (multiherb)	8, 15
Hydrastis canadensis, goldenseal	3	0	0,0
Piper methysticum, kava-kava	3	2 (multiherb)	0,28
Silybum marianum, milk thistle	3	0	23,10
Actea racemose, black cohosh	2	0	15, 0
Curcuma longa, turmeric	2	3	4,3
Crategus spp, hawthorne	2	0	0,38

NOS, or species not otherwise specified, refers to a circumstance in which more than one plant was only recognized as a component (Babos et al., 2021).

From Babos, M. B., Heinan, M., Redmond, L., Moiz, F., Souza-Peres, J. V., Samuels, V., Masimukku, T., Hamilton, D., Khalid, M., & Herscu, P. (2021). Herb-drug interactions: Worlds intersect with the patient at the center. *Medicines* (Vol. 8, pp. 1−19).

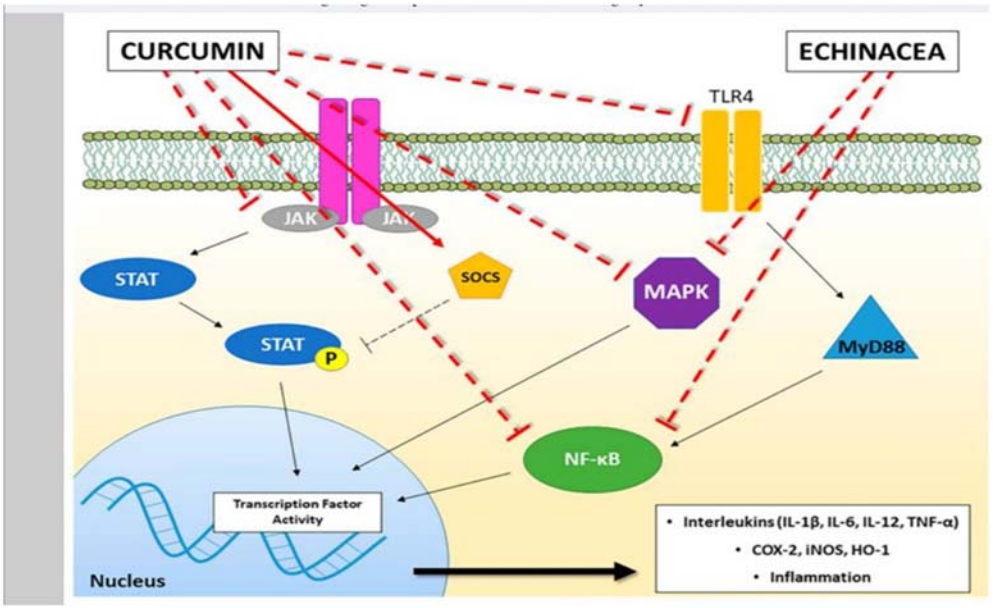

Fig. 12.1 Shows the primary molecular pathways that curcumin and echinacea affect in order to control inflammatory and immunomodulatory activity. The pathway is shown by the solid red line as being activated, whereas the pathway is indicated by the truncated red line as being inhibited. JAK stands for Janus kinase, STAT for signal Transducers and Activators of Transcription, SOCS for suppressor of cytokine signaling proteins, MyD88 for myeloid differentiation primary response 88, NF—B for Nuclear factor kappa B, MAPK for mitogen-activated protein kinase, COX-2 for Cyclooxygenase-2, iNOS for inducible Nitric Oxide (Block & Mead, 2003). *(From Block, K. I. & Mead, M. N. (2003). Immune system effects of echinacea, ginseng, and astragalus: A review.* Integrative Cancer Therapies, *2(3), 247—267. https://doi.org/10.1177/1534735403256419.)*

(Puri et al., 1994). Although some scientific studies seem to indicate that cytokines, which enable effective white cell communication and also modify their activity in particular in preventing tumor growth, are among the many enhanced cell-cell messenger molecules that appear to show this, their exact mechanism of action is still largely unknown. Even while it's unclear why plants would produce these chemicals in the first place, it's likely that, like Actinomycete species, they do so to help plants adapt to environmental and climatic obstacles and show variability. Numerous herbs have been linked to immunomodulatory activity, however Table 12.3 below lists the most widely utilized herbs and their associated phytochemical activities. The remaining portion of this research will first describe the immune system activities that herbal treatments are anticipated to enhance, followed by the most current findings from animal models and human clinical trials on the identified active immunomodulatory principles of certain commonly used herbs. As a result, it could seem to the reader that some plants are not sufficiently covered. For instance, despite the fact that multiple animal research (Harris et al.,

Table 12.3 Many herbs have been linked to immunomodulatory activity, however the most popular ones are included together with their recognized phytochemical activities (Cundell, 2014).

Herb	Activity	Phytochemicals
Allium sp. (chives, garlic, leek, onion)	Anti-tumor	Ajoene, allicin
Aloe vera	Anti-inflammatory,Anti-tumor	Acemannan, aloe-emodin
Asteraceae (*Chamamelumnobile*, *Matricariachamomilla*)	Anti-inflammatory, antitumor	Apigenin, terpenoids, flavonoids
Curcurma longa (curcumin)	Immunestimulant	Curcumin
Echinacea purpurea	Immunostimulant	Alkylamides, glycoproteins
Glycyrrhizaglabra (licorice)	Immunostimulant	Licochalcone A, glycyrrhetinic acid and glycyrrhizicacid (β-GA)
Labiatae family (oregano, thyme)	Anti-tumor	Thymol, carvacrol
Nigella sativa(Black cumin)	Anti-tumor	Thymoquinone
Panax ginseng	Adaptogen	Ginsenosides, gintonin
Tinosporacordifolia	Immunostimulant	Arabinogalactan
Withaniasomnifera (Ashwagandha)	Immunostimulant (anti-tumor)	Withaferin A
Zingiberofficianalis	Immunostimulant	Gingerols

From Cundell, D. R. (2014). Herbal phytochemicals as immunomodulators. *Current Immunology Reviews, 10*(2), 64–81. https://doi.org/10.2174/1573395510666140915213156

1991; Leung et al., 2004) and human clinical trials have examined the wound-healing effects of *Aloevera* gel (Atiba et al., 2011; Maenthaisong et al., 2007; Nyström et al., 2007; Paulsen et al., 2005).

2. The human immune system and phytochemical immunomodulators

The two components of our immune system are innate and adaptive immunity; while they have different effector mechanisms, they are commonly mixed in terms of initiation (Kumar et al., 2011). There are three primary areas of activity for the phytochemicals that have been studied so far. First, proinflammatory cytokines are assumed to be the primary mechanism by which many phytochemicals affect the innate immune system by increasing the activity of phagocytic cells like macrophages and natural killer cells Fig. 12.2 (Hassan et al., 2021).

Additionally, they might start the potent complement cascade, which heightens inflammation and attracts phagocytic cells. Since the innate immune system serves as the body's first line of defense against threats, it also encourages additional activity

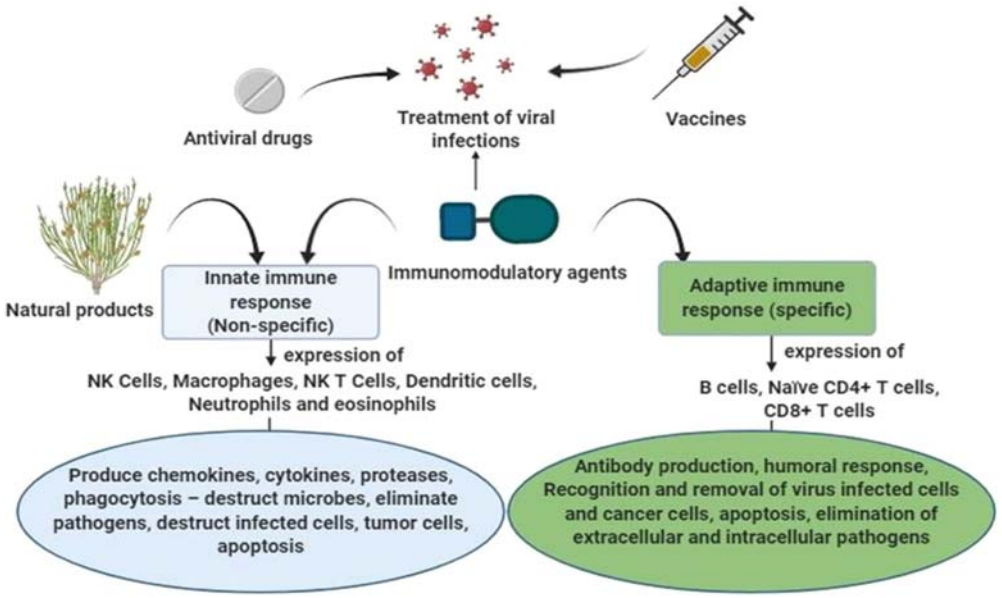

Fig. 12.2 Natural immunomodulators may have a role in the prevention and management of viral infections (Hassan et al., 2021). *(From Abbas, A. K., & Lichtman, A. H. (2012). Chapter 2 Innate immunity; cytokines of innate immunity. In* Basic immunology functions and disorders of the immune system*, 4th ed. Philadelphia (pp. 34–35). Saunders Elsevier Press.)*

such as the manufacture of antibodies (humoral responses) or the stimulation of T cytotoxic cells (cellular responses) (Kumar et al., 2011). Second, some herbs might be useful in the treatment of asthma because they seem to be able to suppress mediators generated by mast cells. They may also hinder the formation of T cytotoxic cells or antibodies through the regulation of cytokine activity, which would quiet a hyperactive immune system (Kumar et al., 2011). Third, using various herbs as tumor inhibitors via various cellular processes is the area with the most potential. Therefore, in order to fully understand the efficacy of the phytochemicals addressed in this study, it will be necessary to first explore the processes driving innate immunity, asthma, autoimmune disease and cancer.

3. Mechanisms of innate immunity involving cell, cytokine, and complement proteins

Natural killer cells, monocyte-macrophages, and neutrophils act as sentinels to guard the entrances to their human hosts (NK cells). The transmembrane receptors called PRRs (pattern recognition receptors) on the host cell connect with PAMPs (pathogen-associated molecular patterns) on the invading cells to engage these cells with a potential danger Fig. 12.3 (Gustavo et al., 2018).

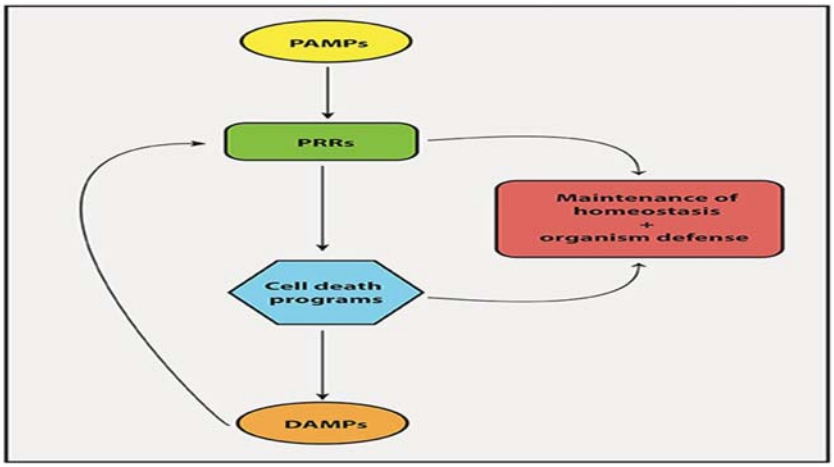

Fig. 12.3 Shows how PRRs and cell death pathways interact. To support tissue homeostasis and host defense against pathogens, the activation of various cell death mechanisms is induced by the engagement of PRRs in response to PAMPs. It's crucial to note that cell death products, also known as DAMPs, create a feedback loop that activates PRRs and causes inflammatory and immunological reactions (Gustavo et al., 2018). *(From Abbas, A. K., & Lichtman, A. H. (2012). Chapter 2 Innate immunity; cytokines of innate immunity. In* Basic immunology functions and disorders of the immune system*, 4th ed. Philadelphia (pp. 34–35). Saunders Elsevier Press.)*

Cell death pathways and PRRs interact. The engagement of PRRs in response to PAMPs triggers the activation of multiple cell death pathways to promote tissue homeostasis and host defense against pathogens. It's important to remember that cell death products, also known as DAMPs, produce a feedback loop that activates PRRs and sets off inflammatory and immune reactions.

Due to their necessity for the pathogen's life cycle and continual presence on its surface, PAMPs are useful identification molecules for immune system cells. Once a pathogen has been located, the invading cells can either be lyzed (by NK cells) or phagocytosed (by monocyte-macrophages). Additionally, a variety of serum proteins that are active in the complement system and that lead to opsonization (increased phagocytosis), inflammation, and lysis can also directly recognize PRR molecules on the surface of invading pathogens and start the process of eradicating them. In the instance of the innate immune system, a hydrolyzed complement component (C3b) may directly attach to target PAMPs. Alternately, microbial carbohydrates may engage complement binding by interacting with the acute phase proteins mannan-binding lectin (MBL) or C-reactive protein (CRP) (Rus et al., 2005). The cell will eventually be destroyed by the commencement of apoptosis as a result of the extra C3 molecules being broken down to generate more C3b molecules when further complement components attach in the order C5, 6, 7, 8, and 9. Fig. 12.4 depicts a complement system diagram.

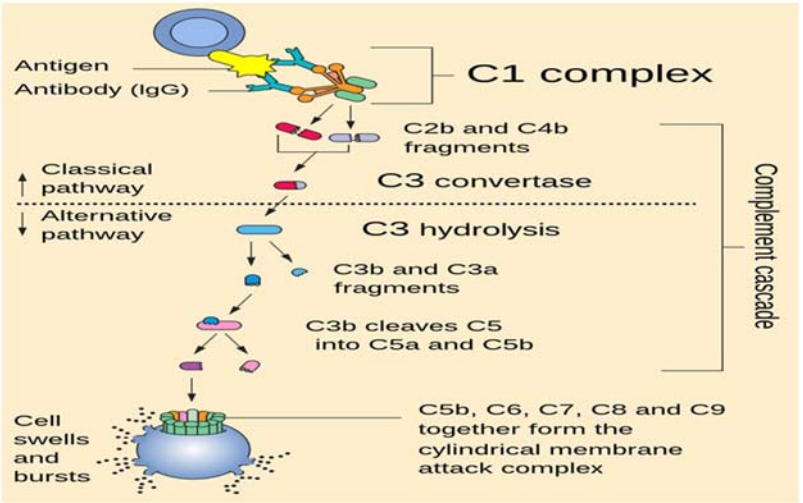

Fig. 12.4 Scheme of the complement system. National Institute of Health (NIH) publication no. 03–5423, September 2003. (*http://www.niaid.nih.gov/publications/immune/the_immune_system.pdf*)

Table 12.4 demonstrates that the increasing aggregate of complement proteins also releases a variety of by-products, including as C3a and C5a, which can both attract neutrophils and monocytes as well as release mediators from surrounding mast cells. Below is a more thorough discussion of these by-products (Abbas & and Lichtman, 2012; Rus et al., 2005).

3.1 Asthma and autoimmune disease as cases of failed adaptive immunity

Asthma's underlying inflammatory state, which has long been known to be caused by the release of mediators from mast cells that have been immunoglobulin-E (IgE)-sensitized, has several important features (Galli et al., 2005). Mast cells, which are present in the skin and mucous membranes of the respiratory and digestive systems, get coated with IgE after being initially exposed to an allergen and then produce highly active biochemical

Table 12.4 A number of by-products are also generated by the expanding complement protein aggregation, including C3a and C5a, both of which have the ability to draw in neutrophils and monocytes as well as release mediators from nearby mast cells (Abbas & Lichtman, 2012; Rus et al., 2005).

Component	Effects
C3a	Inflammation; neutrophil chemotaxis, release of mastcell mediators
C3b	Opsonization and phagocytosis
C5a	Inflammation; neutrophil chemotaxis, release of mastcell mediators
C8	Leakiness of target microbe
C9	Lysis of microbe through holes generated in the cellmembrane

From Abbas, A. K., & Lichtman, A. H. (2012). Chapter 2 Innate immunity; cytokines of innate immunity. In *Basic immunology functions and disorders of the immune system*, 4th ed. Philadelphia (pp. 34–35). Saunders Elsevier Press.

mediators upon further exposures (Galli et al., 2005). The mast-cell-IgE pathway, which is particularly successful in removing helminthic parasites, is subverted in the clearance of pollens, dust, and animal dander because allergens are mistakenly regarded as "little parasites" (Bradding & Arthur, 2016). Fig. 12.5 depicts possible interactions between mast cells and airway immune cells.

Histamine and other short-acting mediators like them, which are smooth muscle constrictors, vasodilators, and overall pro-inflammatory, are produced when mast cells are first activated (Galli et al., 2005). Leukotrienes and prostaglandins, which are denovo mediators made from the phospholipid arachidonic acid, are more significant in terms of the pathophysiology of asthma, according to Hallstrand and Henderson (2010) and Fitzpatrick and Soberman (2001). Through the cyclooxygenase or lipoxygenase enzyme pathways, arachidonic acid can produce highly inflammatory mediators (Fitzpatrick & Soberman, 2001). Leukotrienes (LTs), which are produced by lipoxygenase enzymes and have a variety of pro-inflammatory activities, most significantly contribute to the thickening of the airways, mucus secretion, and bronchoconstriction seen in chronic asthma (Hallstrand & Henderson, 2010). LTs cause a protracted inflammatory response as opposed to histamine, which is quickly eliminated (Hallstrand & Henderson, 2010). Strong evidence supports the notion that LTs cause subepithelial fibrosis, mucus cell hyperplasia, and thickening of the smooth

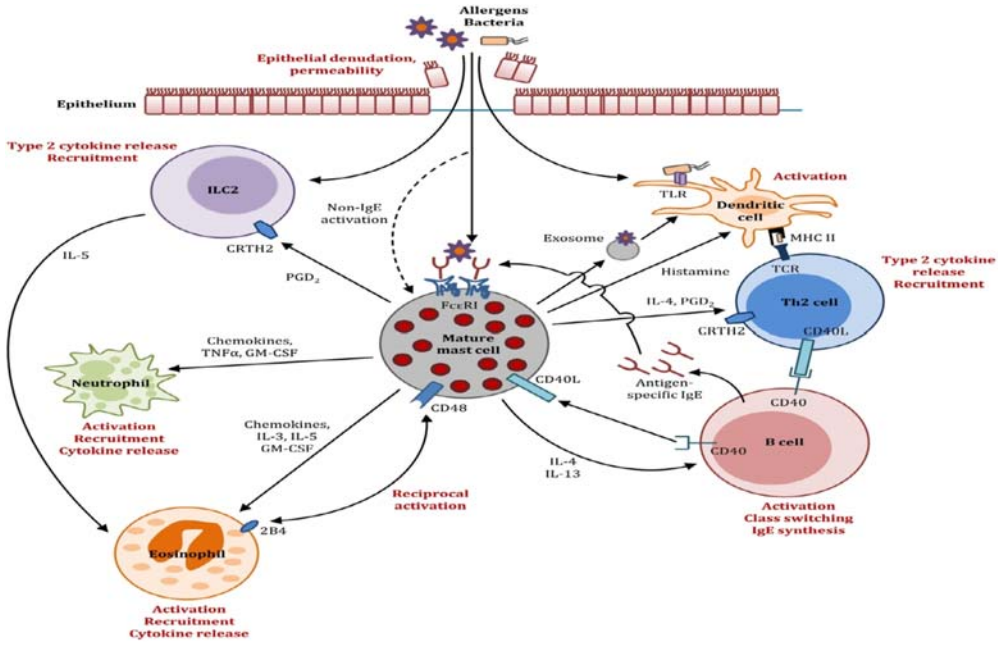

Fig. 12.5 Shows mast-cell IgE pathway. Possible interactions between MCs and immune cells in the airways (Bradding & Arthur, 2015). *(From Bradding, P., & Arthur, G. (2016). Mast cells in asthma - State of the art.* Clinical and Experimental Allergy, 46*(2), 194—263. https://doi.org/10.1111/cea.12675.)*

muscle in the airways (Hallstrand & Henderson, 2010). This is especially true for the so-called CysLTs (LTC4, D4, and E4), which are known to play a significant role in the pathogenesis of asthma by way of chronic airway inflammation, mucus formation and bronchoconstriction (Hallstrand & Henderson, 2010). The pro-inflammatory mediator PGE2, in contrast, is produced via the cyclooxygenase pathway of the metabolism of arachidonic acid, although the amount produced varies on how stressed the cells are (Fitzpatrick & Soberman, 2001). In non-stressed conditions, cells do not accumulate much PGE2, but when cells are repeatedly stimulated, the cyclooxygenase-1 (COX-1) enzyme initially appears, followed by the COX-2 enzyme, which has been associated with chronic inflammation and illness. Additionally, this pathway generates thromboxane (TX) TXA2, which results in the release of serotonin, platelet aggregation, and contraction of smooth muscle (Hallstrand & Henderson, 2010). Limiting COX-2 expression will be just as important for understanding cancer and developmental biology as it has been for understanding inflammation, according to recent study. A few examples of the numerous neoplastic and preneoplastic tissue types that overexpress COX-2 include stomach, colon, lung, and breast malignancies (Fitzpatrick & Soberman, 2001). Therefore, medications that may stop COX-1 and/or COX-2 from activating might be beneficial in the treatment of a variety of inflammatory diseases, such as cancer and allergies. During autoimmune diseases, the body launches a forceful attack against its own tissues that may involve antibodies, cytotoxic T cells, or both, as well as proinflammatory cytokines brought on by their activation, such as TNF- Fig. 12.6.

3.2 Tumor development; adaptive immunity deficit

Because they downregulate antigenic molecules to thwart elimination, are immune to the normal signals of apoptosis seen in damaged cells, and can spread quickly to new sites (metastasize) by encouraging the growth of blood vessels (angiogenesis), tumor cells are frequently particularly difficult for the immune system to combat (Coussens & Werb, 2002). There is evidence that individuals who successfully cure their malignancies have an inflammatory response similar to how a wound heals or how an organ transplant is rejected (Coussens & Werb, 2002). The innate immune system, which is the initial line of defense against foreign invasion, seems to be the last arbiter, therefore the kind of macrophage that is engaged in the early inflammation will essentially determine whether the tumor will survive or not (Sica et al., 2008). The M1 and M2 subtypes of macrophages are distinct. IL-4, IL-10, and IL-6, immunosuppressive cytokines produced by M1 that prevent T-cytotoxic cell activation and promote tumor development Fig. 12.7, as well as Th1 generation and direct tumor cytotoxicity by activating T-cytotoxic cells. They are cytokines that M2 makes.

Tumor associated macrophages (TAMs) secrete proteases that compromise cell basement membranes, enabling the tumor to escape and metastasize (Disis, 2010). It is also

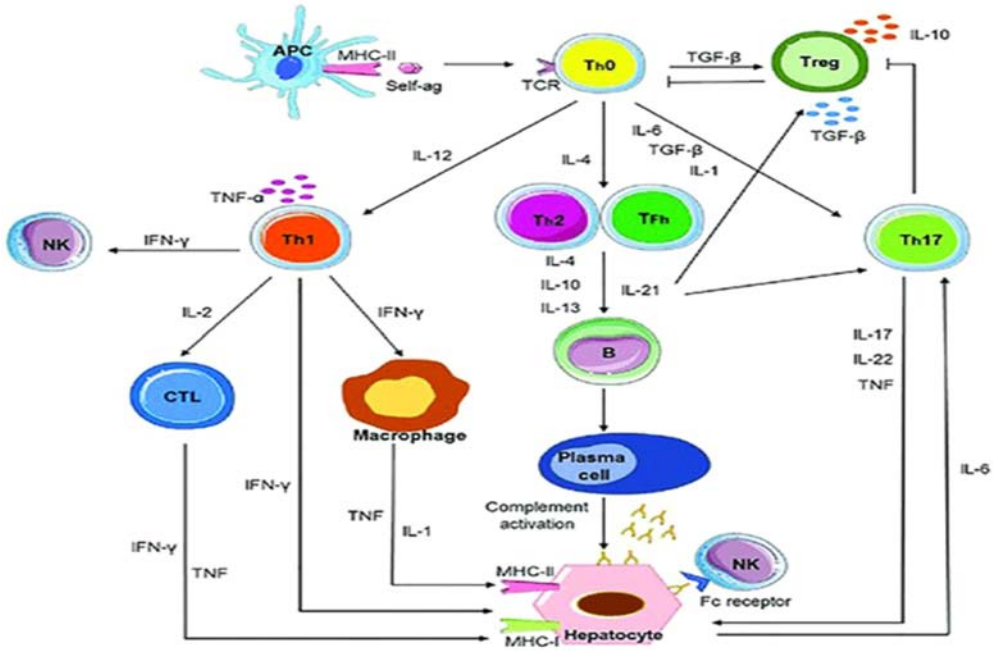

Fig. 12.6 Shows possible hepatocyte autoimmune assault routes in AIH. An immune reaction to liver autoantigens is presumably what causes autoimmune-mediated liver damage in AIH. To stimulate the production of regulatory T cells (Treg), Th1, Th2, and Th17 cells, antigen-presenting cells (APC) deliver autoantigenic peptide to immature CD4 + T helper cells (Th0). These cells then release proinflammatory cytokines (IL-1, IL-4, IL-12, IL-6, and transforming growth factor beta, TGF-b). A cascade of events culminates in the autoimmune attack on hepatocytes as a result of the cytokine releases from each cell group. Through the release of cytokines by Th1 and activated macrophages, liver cell destruction may result from the activation of cytotoxic T lymphocytes (CTL). Th2 cells secrete IL-4, IL-10, and IL-13, which cause B cells to develop into plasma cells, which in turn cause antibody-dependent cellular cytotoxicity and complement activation. TNF-a, IL-17, IL-22, and tumor necrosis factor alpha (TNF-a) are proinflammatory cytokines that Th17 cells emit. They also block Treg cells and induce hepatocytes to secrete IL-6, which further enhances Th17 cell activation. IL-21, a regulator of Treg cell development and Th17 cell growth, is released by Tfh (T follicular helper) cells during the stimulation and differentiation of B cells in antibody-secreting plasma cells.

known that the type of T helper cell secreted, either Th1 (classic T helper cells), which can produce IL-2 and TNF to support cytotoxic T lymphocytes and thereby tumor death, or Th2, which secrete immunosuppressive agents, influences whether tumors will proliferate. These cells also produce angiogenic factors, which promote the creation of blood vessels inside tumors and increase the chance of both their survival and proliferating (Disis, 2010). Last but not least, myeloid derived suppressor cells (MDSC) are also connected to the development of cancer because they are formed when the immune system is under stress and "cope" by producing immature cells. These cells suppress the

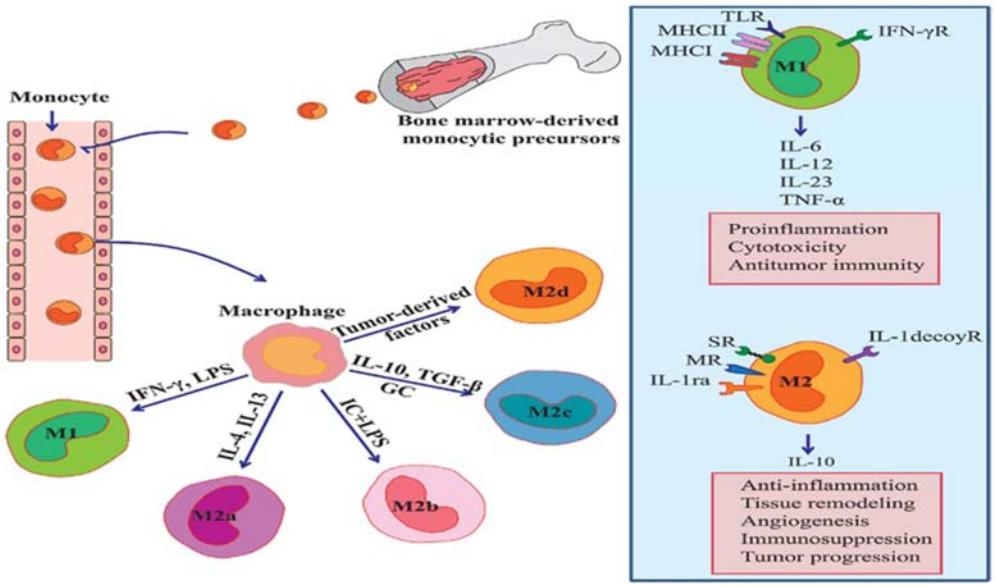

Fig. 12.7 Shows the purpose of macrophage polarization. From circulating monocytes, tissue macrophages develop either a traditional M1 or alternative M2 phenotype depending on microenvironmental cues. IFN- and LPS induce the M1 phenotype, which is characterized by high amounts of pro-inflammatory cytokines such IL-6, IL-12, IL-23, and TNF-. Depending on the stimuli, the M2 phenotype may be split into M2a, M2b, M2c, and M2d. IL-10 production was typically high in M2 macrophages, which also showed high levels of the scavenger receptor, mannose receptor, IL-1 receptor antagonist, and IL-1 decoy receptor. Pro-inflammatory, cytotoxic, and anticancer responses are all driven by the M1 phenotype. The M2 phenotype, in contrast, encourages angiogenesis, immunosuppression, and the growth of tumors. Lipopolysaccharide (LPS), immune complex (IC), glucocorticoid (GC), scavenger receptor (SR), mannose receptor (MR), IL-1ra (IL-1 receptor antagonist), Toll-like receptor (TLR), and major histocompatibility complex (MHC) are all abbreviations.

immune response by a number of means, including by activating T regulator cells, which can reduce inflammation by releasing IL-10 and tumor growth factor beta (TGFβ), and by suppressing specific anti-tumor immunity (Disis, 2010). T-regulator cells are essential for good, functioning immunity because they help to maintain homeostasis and lower the amount of inflammation that may arise after damage or infection (Disis, 2010). Nuclear factor kappa beta (NF—B) expression is essential in determining whether a cell will turn cancerous or not, much as in other chronic inflammatory diseases (Morgan & Liu, 2011). NF—B is essential for managing the cell cycle, ensuring cell survival, and lowering inflammatory responses due to its long-standing involvement in regulating apoptosis and cytokine production (Morgan & Liu, 2011). Therefore, NF—B inhibition inhibits the leukotriene-producing enzymes arachidonate 12-lipoxygenase (LOX-12), arachidonate 5-lipoxygenase (LOX-5), and COX-2 in order to lessen inflammation (Morgan & Liu, 2011). Recent research suggests that the expression of NF—B may also control

the amounts of reactive oxygen species (ROS) in cells (Morgan & Liu, 2011). In phagocytic cells, ROS phagocytes create superoxide and hydrogen peroxide, which promote phagocytosis and intracellular death. Low NF−B expression in cell survival is well correlated with high ROS levels, which are associated with cellular death. A number of models have been used to study potential immune treatments (Balunas et al., 2005). It is important to first assess the efficacy of in vitro cell lines, including the murine macrophage line RAW-264.7 (Lee & Jeon, 2005) and human tumor cell lines, including the HL-60 leukemia (Woelkart et al., 2005), gastric cancer SGC-7901, and hepatocellular carcinoma SMMC 7721 (Peng et al., 2011) cell lines. Next, a variety of animal models are used to assess the immunomodulators' efficacy (Lee & Jeon, 2005). Only until a chemical has been shown to be both safe and effective can it enter clinical trials, and it should be noted that only double-blind, placebo-controlled studies are likely to produce accurate findings in this field. Finally, there is currently very little research utilizing animal models and people on specific herbal components because the majority of the fundamental understanding of the phytochemistry included in this paper has only recently started to emerge over the previous 5 years. Most of the active chemicals described in these two tables are polysaccharide/glycoprotein molecules, terpenoids (including saponins), and flavonoids (Aboughe-Angone et al., 2011; Chu et al., 2012, 2013; Fontes et al., 2014; Rajput et al., 2007; Sharma, 2006). Despite not having been investigated in human clinical trials, alkylamides are known to function in vitro as cannabinoid ligands, binding to CB2 with a similar effectiveness to the endocannabinoids (Woelkart et al., 2005). In fact, Z-tetraene, which makes up 10% of E. angustifolia and 32% of E. purpurea's tetraene isomers respectively, has the strongest affinity (57 nM). Similar outcomes have recently been seen for the sesquiterpene E-β caryophyllene (BC), which is present in oregano, cannabis, and black pepper in high concentrations (Yi et al., 2008). Cannabis (Cannabis sativa), which is chemically similar to BC from oregano, has the ability to selectively bind to the CB2 receptor and is a functional CB2 agonist (Ki = 155 4 nM), according to study by Yi et al. (2008).

4. Immunomodulators identified as herbal phytochemicals

Biochemists began to notice patterns for the elements of the plants used in traditional remedies as they examined and isolated the chemically active molecules at the center of their action. Examples of important classes of phytochemicals with chemoprotective, immunomodulatory, and adaptogenic activity include flavonoids, which include flavones (Sharma, 2006), terpenoids (Thoppil & Bishayee, 2011), saponin (Rajput et al., 2007), and plant polysaccharides (pectic and arabinogalactan) (Aboughe-Angone et al., 2011). These compounds are found in the common herbs listed in Table 12.2.

4.1 Antioxidants, adjuvants and flavonoids

Flavonoids, which have been found in plants in at least 4000 different varieties, are significant components that contribute to the color of the leaves and flowers as well as being immunomodulators (Ledezma et al., 2000). They belong to a group of phenolic substances called cinnaminic acids (coumaric, caffeic), quercetin, flavonoids (flaveones, isoflavones, flavonols, flavanols), and anthocyanins that are produced via the shikimic acid pathway. As antimicrobial agents and communication molecules between plants and microbes, flavonoids are expected to play crucial roles in plant survival. As a result, they perform many of the same tasks as antibiotics in Actinobacteria (Challis & Hopwood, 2003). Flavonoids are distributed differently in different plants; whereas flavones, such as apigenin, the active phytochemical in chamomile, predominate in grains, green vegetables, and herbs, flavonols, such as quercitin, are found in leafy vegetables, apples, and onions (Waksman et al., 2010). Since these phytochemicals have antioxidant activity and are free radical scavengers, they may be helpful in the treatment of cancer and aging. This has attracted a lot of pharmacological interest (Waksman et al., 2010). Apigenin has been the subject of the most research and may be effective in suppressing tumor growth (Wang, I-Min, & Sesso, 2009; Wang, Rayburn, et al., 2009). Apigenin, which is present in chamomile, oregano, and licorice in large amounts, has the potential to suppress TNF-intracellular adhesion, which promotes tumor metastasis, and it may also have anti-angiogenesis properties (Patel et al., 2007). In vitro tests on cell lines of the skin (melanoma), breast, cervix (HeLa cells), colon (Wang, I-Min, & Sesso, 2009; Wang, Rayburn, et al., 2009), and most recently, bladder, showed that apigenin is effective at inducing apoptosis against a variety of malignancies (Patel et al., 2007). However, the effectiveness of it has been tempered by animal breast cancer models (Zhu et al., 2013). Since these phytochemicals have antioxidant activity and are free radical scavengers, they may be helpful in the treatment of cancer and aging. This has attracted a lot of pharmacological interest (Waksman et al., 2010). According to studies on mammary tumors, ingesting the flavonoid enhanced tumor multiplicity while decreasing tumor incidence (Zhu et al., 2013). This is contrary to studies in which the flavonoid was delivered intraperitoneally. Additionally, this medication has not yet undergone clinical testing. Flavonoids may serve as adjuvants, according to recent investigations (Mafuvadze et al., 2013). These effects may help to partially explain the efficacy of herbs and plants that contain flavonoid moieties as well as their ability as chemoprotective species. Last but not least, luteolin, a flavone produced from chamomile, has been shown to have the capacity to alter the inflammatory environment of the brain, particularly in situations of altered brain chemistry (Nworu et al., 2010). First of all, it has been shown to mimic the effects of brain-derived neurotrophic factor (BDNF) and to prevent the production of microglial IL-6 (Meyer et al., 2011; Nworu et al., 2010). Studies have shown that these compounds, when discovered in the maternal blood, are associated to a shift in the

development of the fetus's brain, which may be linked to the development of the offspring's bad social behavior. Additionally, the STAT3 signaling pathway affects luteolin's inhibitory effects on IL-6 production, which in turn prevents autistic-like behavior in mice Fig. 12.8 (Jang et al., 2010).

Thirdly, it has been discovered that luteolin reduces the inflammatory environment associated with multiple sclerosis in patients by inhibiting the mast cell-dependent activation of activated T cells and activated peripheral blood mononuclear cells (Parker-Athill et al., 2009). These findings have all prompted scientists to hypothesize that luteolin may be useful in treating autistic people' seizures as well as the neuro-inflammatory symptoms of their disease (Sternberg et al., 2009). In contrast to the previously stated study of A. chordifolia, which revealed that Pinusmaritima flavonoids were definitely pro-inflammatory, Theoharides et al. (2011) discovered that these flavonoids from Pinusmaritima counteracted inflammation by reducing cytokine production (Mafuvadze et al., 2013). This makes it much more difficult to evaluate data based on flavonoids as distinct compounds. Variations in the individual flavonoids that make up the extracted mixture and control overall potency may be the cause of this. Ibrahim and colleagues' recent work (Cho et al., 2001) suggests that it may have something to do with the conditions

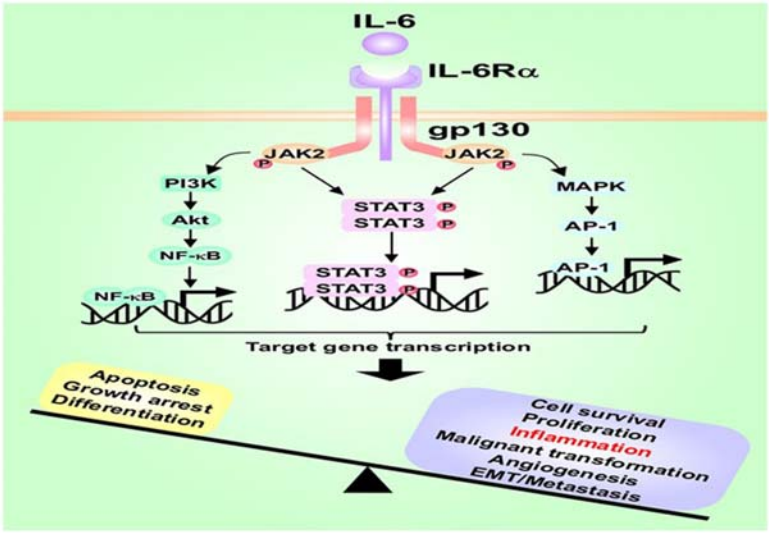

Fig. 12.8 Illustrates the function of the IL-6/STAT3 signaling pathway in hepatocarcinogenesis and how it interacts with other pathways. When Kupffer cells or hepatocytes secrete IL-6, it binds to IL-6R and causes it to homodimerize with gp130. This triggers the activation of downstream signaling pathways like JAK/STAT3, PI3K/Akt, and MAPK pathways, which encourage cell growth and survival, inflammation amplification, and tumor invasion and metastasis (Jin et al., 2015). *(From Jin, K., Li, T., Sánchez-Duffhues, G., Zhou, F., & Zhang, L. (2017). Involvement of inflammation and its related microRNAs in hepatocellular carcinoma.* Oncotarget, *8(13), 22145–22165. https://doi.org/10.18632/oncotarget.13530.)*

in which the plants were raised. These researchers demonstrated that when more nitrogen was added to the soil, the overall phenolic and flavonoid contents of plants decreased, with the majority of the decline occurring in the leaves and shoots. On the other hand, it was shown that the synthesis of these secondary metabolites was enhanced by high carbon dioxide levels. Harvesting and cultivation techniques are essential. Finally, it's possible that flavonoids continue to play an immunomodulatory role, which means they only enhance immune function in species with a weak or overactive immune system, such the naturally immunosuppressed C57BL/6 mouse (Mafuvadze et al., 2013).

4.2 Terpenoids, saponins; importance in cancer and the chronic inflammatory environment

Terpenoids, which have over 30,000 members and are frequently specific to each plant species, are one of the largest families of natural botanical phytochemicals (Ibrahim et al., 2011). Additionally, these compounds can transform into sesquiterpene and triterpene saponins via the squalene pathway (Dubey et al., 2003). The hypothesis that these phytochemicals' activities are largely through the prevention of a "faulty" innate immune inflammatory response, which is the hallmark of the development of neoplastic illness, has gained support from studies on the efficacy of these substances in the treatment of cancer. Many herbal remedies are effective because they include mixtures of terpenoids and/or saponins (see Tables 12.3 and 12.4). Like their larger counterparts, monoterpenes have chemoprotective properties. Thymoquinone (Khan et al., 2011) is particularly noteworthy in this regard because it has been demonstrated to have the ability to inhibit cancer cells by producing IL-6 and degrading IF-B to prevent NF—B activation. Another fascinating monoterpene is carvacrol, and research in multiple animal models has demonstrated that it can promote "healing" by lowering the production of TNF- and FoxP3+ regulatory T cells (Silva et al., 2012). A mouse model of PG-induced arthritis was used in studies by (Wieten et al., 2010) that showed the monoterpene increased the expression of heat shock protein 70 (Hsp70) on the Peyer's patches and improved their interaction with T cells. Furthermore, carvacrol therapy increased the number of regulatory T-cells ($CD4^{+}CD25+FoxP3+$) both locally in the joint and systemically in the spleen, and virtually completely prevented proteoglycan-induced experimental arthritis (Wieten et al., 2010). Using a mouse bone marrow model of RA (Spiering et al., 2012), reported findings that were comparable (thermal stress). These researchers demonstrated that carvacrol and temperature stress caused the synthesis of mRNA for both pro- and anti-inflammatory mediators. Spiering et al. (2012) found that dendritic cells (DC) with this mixed profile were more likely to be FoxP3+ regulatory T cells and less able to activate proinflammatory T cells. Carvacrol is a unique molecule because of the inflammatory environment, however there haven't yet been any human therapeutic trials or pilot research. Tumor cells are frequently particularly difficult for the immune system to combat because they downregulate antigenic molecules to thwart elimination,

are resistant to the normal signals of apoptosis seen in damaged cells, and are able to grow quickly and spread to new sites (metastasize) by promoting the growth of blood vessels (angiogenesis) (Coussens & Werb, 2002). Thoppil and Bishayee (2011) claim that a number of the triterpenoids that are now understood have the ability to prevent the proliferation of tumor cells in vitro (induction of growth phase arrest) or induce apoptosis through a variety of mechanisms (increase in P53 gene expression, apoptotic protein levels). A potential mode of action for the terpenoids may be the suppression of HMG-CoA reductase. Since cholesterol is necessary for proliferative tumor cells to develop, this technique effectively "starves" the tumor of nutrients (Chow et al., 2002). Terpenes can aid in the prevention of tumor development by fostering the protective phase II enzyme glutathione-transferase (GT). GT reduces the quantity of harmful compounds present in cells by converting dangerous chemicals into ones that the cell can readily remove. There are a number of terpenes having GT action, but limonene, geraniol, and carvone are those found in the well-known plants of the Lamiaceae and Umbelliferaceae families (Elson, 1995). Another way to treat tumors is using saponins, which, unlike their triterpenoid brothers, work by serving as adjuvants—substances that increase immune reactivity without participating in the response (Zheng et al., 1992). Triterpenoids that have had a steroid or triterpenoid aglycone and one or more sugar chains added are known as saponins (Rajput et al., 2007). Both pro-inflammatory cytokines, particularly IL-2, and robust T cytotoxic cell responses against mucosal antigens have been demonstrated to be induced by them (Zheng et al., 1992). Ginseng's primary phytochemical activity is mediated by ginsenosides, which are saponins that are abundant in the root system of the plant (Xin-Mei et al., 2012). Both Korean (Panax) and American ginseng contain more than 100 distinct ginsenosides, and much is known about the links between their structure and action (Li et al., 2009; Liu, 2005).Studies have shown that ginsenoside molecules' anticancer activities rise as the number of their sugar moieties falls; molecules with four or more sugar residues are ineffective (Liu, 2005), and molecules with three or fewer sugar residues only have marginally stronger inhibitory effects (Li et al., 2009; Liu, 2005). Ginsenosides without any sugar residue exhibit the strongest anticancer efficacy of these substances (Li et al., 2009). Ginsenosides' anticancer potential has also been shown to increase when the double bond at C-24/25 is removed and hydroxyl or methoxyl is added to the C-25 position (Wang, I-Min, & Sesso, 2009; Wang, Rayburn, et al., 2009). As a result, an increase in the chemical's hydrophobicity is associated with increased absorption by cancer cells. Astragalus also contains cycloartanesaponins, a particular family of low molecular weight chemicals unique to this species and precursors to phytosterols (Qi et al., 2010). Although tumor inhibition and apototogenic activity are believed to be among astragalus saponins' non-immunological qualities (Mamedova & Isaev, 2004), the efficacy of their wound healing is what matters most. In a ground-breaking work, Sevimli-Gür and associates examined the four cycloartanes in Turkish astragalus' capacity to hasten the healing of

full-thickness wounds in Sprague—Dawley rats and cell culture assays both in vivo and in vitro. Using purified samples of the four cycloartanes, astragaloside IV, cycloastragenol, cyclocephaloside I, and cyclocanthoside E (0.001—100 ng/mL for the in vitro study and gels ranging from 2.5% to 10% for the in vivo study), the authors discovered a dose-dependent increase in cell viability and wound healing efficacy. Last but not least—and probably most importantly—it has been proven that saponins may penetrate cell membranes by reacting with cholesterol and forming pores or holes. In this latter aspect, they may mimic complement-induced damage, which is typically initiated against a bacterial cell during innate immunity, or they may help T cytotoxic cells function more effectively by increasing antigenic exposure (Wang et al., 2013).

4.2.1 Multifaceted immunomodulatory activities of 1,8-cineole as a case in point for monoterpenes

Cineole, also known as 1,8-cineole or 1,8-cineol (also known as eucalyptol), is present in the essential oils of numerous plants, most notably eucalyptus, but is not included in this monograph because it is a tree rather than a herb (Sjolander et al., 2001). Its emphasis is warranted because many of its functions are shared by other terpene compounds. Numerous animal models have been used to demonstrate the efficacy of 1,8-cineole. The anti-inflammatory effects of 1,8-cineole (0.15 and 1.5 g/mL) on decreasing polyclonal-stimulated cytokine production by unselected human lymphocytes and LPS-stimulated monocytes were also investigated in this study. The monoterpene 1,8-cineole considerably decreased the production of cytokines in lymphocytes (by 92%), monocytes (by 99%), IL-1 (by 84%), IL-4 (by 70%), and IL-5 (by 65%) at the higher dose (Bhattacharjee et al., 2012). It was also efficient at reducing the generation of TNF- and IL-1 by monocytes and lymphocytes. These results were verified and extended by Juergens team (Youjinet al., 2006), who were also able to show that 1,8-cineole could inhibit lipopolysaccharide (LPS)- and interleukin 1 (IL-1)-stimulated mediator production by human monocytes in vitro, demonstrating a decreased production of TNF-, IL-1, LTB4 and TXB2, all mediators that are highly prevalent in asthma and other inflammatory diseases (COPD). In addition, 1,8-cineole was shown to be able to suppress arachidonic acid metabolism in blood monocytes of asthma patients, as measured by LTB4 and PGE2 generation (Juergens et al., 2004).

4.3 Plant cell wall polysaccharides; hemicelluloses, pectin sand arabinogalactans

Plants have a wide range of chemicals called polysaccharides, the majority of which are found in intricate cell wall components. Cell wall components may be divided into three groups: cellulose, hemicelluloses, and pectin. Pectin and most of these hemicelluloses have been linked to immunomodulatory properties. Hemicelluloses are made structurally of a β-linked sugar backbone and are called after the sugars that make up its backbone, such

as xylan, which is β-1,4-D-Xylose. Other hemicellulose kinds include mannans, xyloglucans, and glucomannan Fig. 12.9 (Benaimeche et al., 2020).

Acemannan, a polymannose that has been β-(1,4)-acetylated, can speed up the healing of wounds, burns, and ulcers. Recently, it has also been demonstrated that hemicellulose stimulates cemento-cytes' production of collagen, which suggests that it may help treat periodontal decay, a problem that is currently widespread around the world. According to Petersen and Ogawa (2005), the second class of immunomodulators found in plant cell walls includes homogalacturonan, a linear polymer that accounts for about 65% of all pectin, rhamnogalacturonan II (RG-II), a substituted form of HG that accounts for 10% of all pectin, and rhamnogalacturonan I (RG-1), which accounts for the remaining 4%. Since its breakdown results in (Mohnen, 2008). Furthermore, when side chains richer in arabinose or galactose are added, the galacturonan chain may experience further substitutions, notably in the case of RG-I. First off, immune-stimulating pectins frequently feature higher levels of neutral monosaccharide molecules and less galacturonicresidues (less than 75%). Moreover, since terminal residues of ß-D-glucuronic acid are present. Not to mention, stimulation can target cell-based responses like monocyte-macrophages and T cytotoxic cells or it can enhance the production of antibodies via B lymphocyte stimulation. Pectins have also long been recognized to be able to both stop and slow the growth of cancers, particularly colon tumors (Leclere et al., 2013). Popov and Ovodov (2013) claim that the chemoprotective action of pectins includes binding and sequestering carcinogens in the gut and activating the p53 apoptotic pathway in colonic epithelium when butyrate is converted by colon bacteria (Sanders et al., 2004). Pectin's anti-tumor properties are enhanced when it is subjected to alkaline, followed by acidic pH values that result in arabinogalactans and galactans. Arabinogalactans are normally present in low quantities in plants and make up less than 1% of the dry weight of the cell material. They are typically high carbohydrate (90%) and low protein (10%) molecules. Arabinogalactans, however, have been found to have strong effects on phagocytic cells, the creation of pro-inflammatory cytokines, the augmentation of NK cell cytotoxicity, and the ability to activate both complement pathways. Analysis of the structure-function link reveals that arabinose is required for complement fixing

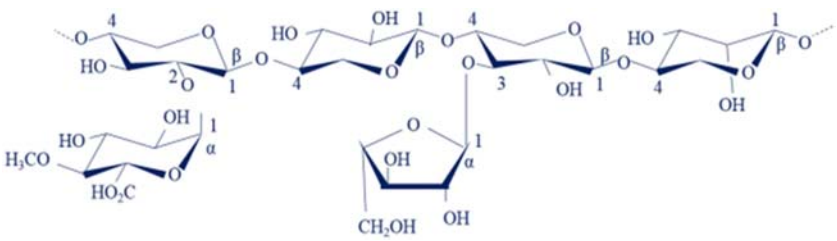

Fig. 12.9 Shows the Hemicellulose (xylan) has a xylopyranose backbone and side branches containing glucuronic acid (1, 2) and arabinofuranose (1, 3).

activity (Kim et al., 2002). The optimal complement activating structure, or AG-II structure, is thought to be composed of separate 1,3 and 1,6 linked galactose chains with branch points at the 1,3,6 positions. These two species of arabinogalactans, E. purpurea and B. tinctoria, have recently been demonstrated to elevate serum properdin levels and enhance the effects of larch arabinogalactan. They include this type of structure. These results point to a different mechanism for complement activation. Pectin-rich polysaccharides from Panex ginseng (RGAP/ginsan), which have immune-stimulating and anticancer properties, have also gained interest (Kiyohara et al., 2010). RGAP/ginsan stimulated mice peritoneal macrophages to kill murine melanoma B16 tumor cells when combined with IFN. The pro-inflammatory cytokine production increased concurrently with the activation of the NF—B pathway to increase tumor killing (Park et al., 2006). Similar NF—B pathway stimulation findings were shown with Astragalus polysaccharides, which also have the unique capacity to stimulate cathelicidins, molecules found in bone marrow progenitor cells as well as mature neutrophils and crucial to the innate immune response to infection.

4.4 The chromones: New plant molecules

Over the past several decades, an unique series of cyclooxygenase pathway inhibitory chemicals have been extracted from the C-glucosylchromones in Aloevera gel (Choi et al., 2008). The three chromones that have been most fully studied in connection to the anti-inflammatory qualities of aloevera are aloeresin, aloesin, and barbaloin (Patel et al., 2012; Speranza et al., 2005). Benzene and -pyronerings are combined to generate phenolic compounds known as chromones. All are significantly concentrated at the leaf margins and are all present in high concentrations in early, growing Aloe Vera leaves (Patel et al., 2012). Barbaloin was initially discovered in 1956, followed by aloesin, which was first characterized in 1970 and is believed to be the parent chemical of the aloe chromones (Choi et al., 2008), and aloeresin (Speranza et al., 2005). Studies conducted on aloesinchromone derivatives (Yagi et al., 2002) revealed that they were able to inhibit TXA2 synthase in addition to COX-2. In 2005, Sparanza and colleagues demonstrated the potent anti-inflammatory properties of both aloesin and aloeresin utilizing the mouse ear croton oil paradigm. Based on these studies, the authors proposed that the p-coumaroyl group, which is present in aloesin but absent from aloeresin II, played a role in the structure-function relationship, similar to earlier studies by (Gutterman & Chaucer-Volfson, 2000). Data from two important studies (Yagi et al., 2002) suggest that chromones may have phosphodiesterase (PDE) enzyme inhibitory action. Early studies by Nakagomi shown that the histamine release from rat mast cells was potently inhibited by barbaloin when release was triggered by calcium dependency, but not when release was caused by calciumin dependence by the mitogen canavalin A (Yagi et al., 2002). These results point toward a PGE route. 21 chromones from Aloe vera gel were recently discovered (Zhong et al., 2013), and it was demonstrated that they

exerted their effects via suppressing PDE, especially PDE4D. PDE4 enzymes help in the breakdown of cyclic AMP to 5′AMP, which can activate inflammatory cells or, in the case of mast cells and basophils, cause degranulation. First, anthraquinones with glucosyl groups on the C-10 of the ring demonstrated decreased PDE4D inhibition (perhaps due to stearic hindrance). Thirdly, it was discovered that pyrones with a p-coumaroyl ester had a potent inhibitory effect on PGE4D. The 5-hydroxymethyl and 7-methoxygroup-containing chromoneaglycones and their enhanced PGE4D activity were the second and third findings, respectively. PDE4 and COX-2 inhibitors are likely to be beneficial for treating autoimmune illnesses and asthma, and structure-function investigations like those in the listed research may discover overlapping structures that are efficient in both situations, such as the p-coumaroyl group (Speranza et al., 2005).

5. Conclusion

This review's ability to accurately depict the immunomodulatory effects of herbal treatments used by millions of people throughout the world has been hindered by a lack of consensus about the bioactive ingredients and the performance of successful human clinical trials. These difficulties, and some possible future paths, will be discussed in the monograph's concluding section. It's crucial to emphasize the advantages of using herbs as conventional treatments before examining the drawbacks of using them as pharmaceuticals. First, the general public often believes that most herbs and herbal extracts are less hazardous than many popular modern conventional pharmaceutical medicines. Misidentification or alterations in the herbal composition can also lead to misadventures with plants. For instance, early problems with the use of *Echinacea* stemmed from its popular name, "Missouri snakeroot," which it shares with another plant, *Parthenium integrifolium*. In fact, compendia by various herbalists show that due to misidentification, a large portion of the early studies on the therapeutic benefits of *Echinacea* were really done on *Parthenium integrifolium*. In some cases, it is also advisable to employ herbal remedies with caution. Examples include the noteworthy estrogenic effects of *ginseng*, the heart-attack-causing β-sitosterol found in *aloe vera*, and the link between glycyrrhizin use and failure. Second, the immunomodulatory properties of some herbal items can be combined with their usage as a drug delivery method due to their ease of skin penetration. This holds true for terpenes like D-limonene and 1,8-cineol, which, respectively, 23 and 95-fold more efficiently improve the skin's permeability to the chemotherapeutic medication 5-fluorouracil through skin and mucosal membranes. The adjuvant qualities of different saponins, astragalus extracts, and fructans from garlic constitute the third factor. Fourth, many plants contain substances referred to be adaptogens, including 18-Glycyrrhetinic acid, anolides, and ginsenosides, which can boost the inflammatory response to infection and promote healing while reducing chronic inflammation. No conventional drug has adaptogenic qualities. Ragrapholide is an astragalus compound

with particular therapeutic characteristics that can stimulate cathelicidins. Paniculata inhibits NF—B activation by the covalent modification of reduced Cys62 of p50, and carvacrol from oregano oil interacts with T regulatory cells and heat shock proteins. Therefore, they have the potential to be used as pharmacological medications in the future, either directly or in a semi-synthetic form. Despite growing investment in research, the two main barriers to growth are the quality, standardization, and health claims of herbal products as well as global variance in regulation. Most countries classify herbs as food supplements, however again, the regulations controlling this license vary. According to the Dietary Supplement Health and Education Act of 1994, herbs are considered dietary supplements in the United States, and the Food and Drug Administration (FDA) does not have to approve of their marketing. A novel ingredient's composition and safety must be examined, while those that have been in use since before 1994 do not. Not to mention, the 2004 European Directive requires all herbal medicines in Europe be registered and subject to national control. Verification of usage for at least 15 years outside the European Union or 30 years inside is necessary for registration. In order to avoid contamination by other substances, phytomedicines are also precisely measured and prepared, exactly like conventional medications. There is stricter implementation of numerous international regulations in Europe, where monographs on the harvesting and processing of herbs specify how phytochemicals are produced, leading to varying product control. Although it has already been established that the inconsistent nature of early Echinacea products was brought on by incorrect speciation, it also seems likely that the products' ineffectiveness was brought on by dubious components. In fact, a study of 59 Echinacea formulations sold commercially revealed that six (10%) of them had no detectable Echinacea. Additionally, the species content matched the label in 31 (52%) of the samples. Finally, 9 (43%) of the 21 standardized preparations fulfilled the label-described quality criterion. Since it appears to be the most beneficial, immunologically, some scientists have advised using alkylamide content as the standard component to optimize the therapeutic effects of this plant and possibly also provide its talents medical legitimacy. Aloevera appears to be experiencing problems with standardization as well. In just 9 out of 18 commercial aloe vera products was the beneficial Acemannan polysaccharide detected. The isomers of oregano oil, thymol and carvacrol, as well as the ginsenosides and gintoins of Panazx ginseng are examples of antagonistic chemicals, although the majority are complementary. Depending on how the herbs are processed, the product may have an anti- or pro-inflammatory impact, or it may have no effect at all. Studies on the issue have shown that aging is best for garlic extraction, as opposed to chamomile, where alcohol extraction maintains flavones and an aqueous extract concentrates the apigeninglucosamides. Additionally, many of the plants' active ingredients may be lost if they are consumed. For example, even when taken in quantities as high as 8000 mg, curcumin may not reach 2 M levels in the blood stream. Similar to how Echinacea contains a variety of chemicals, research has shown that only the alkamides are

beneficial after intake and may even need digestion. Murine macrophages (RAW 264.7) and human neutrophils from healthy individuals only generated pro-inflammatory cytokines (TNF-, IL-1, IL-6 and IL-10), and NO when exposed to a simulated digest or a fresh extract of EP. Alkylamides from EP are broken down by liver microsomes more quickly than those from EA (during first pass metabolism in the liver), but when these two species were combined for consumption, EA slowed down EP's liver metabolism. Last but not least, in order for some herbs to be absorbed, they may need to be ingested in combination. Most importantly, the amount of phytochemicals an extract contains ultimately depends on the plant from which it was manufactured. It has been proven that harvesting methods and seasonality have an effect on plant phyto-chemistry by a superb analysis of the natural wild Echinacea harvest. According to a study by Qu and colleagues, newly matured seed heads (NMSH) and tips of EP roots contained around 14.4%, 1.54%, and 0.77%, respectively, of alkylamides from the plant Echinacea, which have been proven to be more common in roots. Interestingly, the powerful Z-isobutylamide made up just 9.4% of the alkamides in roots, but made up 87.9% of NMSH and 76.6% of young tops. Additionally, researchers discovered that dried EP plant roots often contain more alkylamides than extracts, demonstrating the value of gathering and preserving plant material. It is estimated that 15,000 of 50,000—70,000 medicinal plant species are already in risk of extinction as a result of the impacts of employing natural, wild plants in this way. The International Cooperative Biodiversity Group (ICBG) was established in 1992 with the goal of integrating pharmacological research, biodiversity conservation, and development. In an effort to discover novel phytochemicals, they devote a lot of time to collecting, extracting, and detecting active moieties in different plant species from across the world. Then, as was already indicated before in this study, these are first evaluated using bioassays and then in cell lines. The process of creating novel medications is challenging and needs significant in vitro investigation of the mechanisms of action, in vivo testing on animals, and eventually human clinical trials, which are comparable to those previously carried out for natural products like antibiotics. The development of a new drug may be quite costly, taking 10 years and costing $800 million. However, processing huge volumes of plant material for little amounts of immunomodulatory compounds is not likely to be viable in practice, aside from being wasteful, given the potential need for non-toxic, effective, and distinctive alternative medications from plants. Thus, a further approach for drug development in the herbal realm is presented through the use of combinatorial chemistry to assess and optimize structure-activity correlations. Recent structure-activity links have been made between aloe vera aloes in and anthroquinones, licorice's 18-glycyrrhetinic acid, and ginsenosides from Panax ginseng, opening the way for the development of semi-synthetic and synthetic versions. Only recently have the first curcumin analogs been discovered. EF-24 has recently been shown to be effective as an NF—B inhibitor and apoptosis inducer of in vitro tumor cells as well as for an in vivo mouse model against DU145 prostate cancer xenografts, with IC-50 values of less

than 1 M across a range of breast cancer cell lines. Researchers have also developed a curcumin-loaded silk fibroin nano-specific delivery system that has been shown to have enhanced uptake, intracellular residence duration, and effectiveness against HER2-positive MDA-MB-453 breast cancer cells. Once all the structure-activity links have been established, individual moieties have been purified, and their bioavailability has been identified, it is imperative that the ultimate human trials include patient randomization, be double blind, and be placebo controlled (double-blind RCT). The reader may find various trials when this is not the case by searching, but AS, only a small number of these have been conducted. Why is this aspect of the study so important? Simply put, observer and patient bias. Due to the great demand to publish research, this type of experimental design has become the benchmark for generating reliable data that is respected by reviewers. According to Kaptchuk, who examines this approach in a 2001 study, the double-blind RCT may not be objective in a realist sense, but rather is objective in a "softer" disciplinary meaning. However, it remains the standard that must be attained in order to provide reliable data. Similar to the range of synthetic and semi-synthetic forms that are currently available, where their absorption and bioavailability have been enhanced while reducing their negative effects, antibiotics had to travel a similar journey when they were originally found in natural mold cultures in 1928. Several antibiotics might not have become widely used if not for these modified versions. For instance, tetracycline, a medicine with poor absorption and unfavorable side effects, was converted into doxycycline, a well-known broad-spectrum semi-synthetic treatment. Similar to how combinatorial chemists made erythromycin go from being the ugly duckling to the swan, azithromycin is now a well-known medication. In many ways, the evolution of the phytochemicals included in this book is comparable to the early phases of antibiotic discovery, when it took 20 years to stabilize and enhance penicillin action. The good news is that finding and developing herbal medicines for use in the future only requires closely knit teams of botanists, biochemists, combinational chemists, and immunologists thanks to advancements in in vitro quick throughput, bioassays, genetic sequencing, and cloning technology since then. The significance of ethnobotanists like Kelly Kindscher must also be underlined since knowing how natural plants are utilized today requires knowledge of the prehistoric societies that were the first to discover and use them. Increasing scientific understanding and proof of medicinal photochemistry may cause herbs or their derivatives to transition from conventional, supplementary medicine to mainstream medicines.

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CHAPTER 13

Medicinal plants and other autoimmune diseases

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1. Introduction

The immune system of the human body is crucial in defending against the assault of harmful germs. The immune response can be divided into two types, Humoral or antibody-mediated immunity and cell-mediated immunity. Similar to that, immunosuppressive activity describes a decrease in the immune system's activation (Abass et al., 2012). Multiple diseases in humans are caused by immune system imbalances. So, the immune-suppressants are applied to monitor the symptoms of allergic, autoimmune and organ transplantation related disorders. Autoimmune illnesses include psoriasis, celiac disease, rheumatoid arthritis, myasthenia gravis, systemic lupus erythematosus, Crohn's disease, and ulcerative colitis, whereas organ transplants involve bone marrow, the heart, kidney, lungs, and liver (Hong & Kahan, 2000). Medical herbs function as immunosuppressive drugs due to their immune system-inhibitory, cellular, and humoral immunological responses (Halloran, 2004).

Autoimmune illnesses are brought on by dysregulated immune responses that attack the body's own tissues rather than performing their normal defense against external pathogenic invaders. In the etiology of autoimmune disease, genetic and environmental variables interact in intricate ways (Viatte et al., 2013; Pollard, 2015). Cells or antibodies mediate the inflammatory responses and damage to atherosclerotic tissue (Comerford et al., 2014; Mihai & Nimmerjahn, 2013). There are two types of autoimmune disorders, Systemic (affects whole body in general) and organ-specific (affects a particular organ) (Comerford et al., 2014; Crown et al., 2015). Rheumatoid arthritis (RA), type 1 diabetes (T1D), and systemic lupus erythematosus (SLE) are the primary autoimmune diseases that afflict people (Comerford et al., 2014; Crown et al., 2015). Industrialized nations often

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have a greater frequency of these illnesses than impoverished nations. In the United States, the prevalence of RA is thought to be around 1%, compared to 0.2%–0.3% in China and a subgroup of the population from rural South Africa, according to Mackie et al. (2006). Additionally, the proportion of women to men with RA is around 2–3: 1 (Table 13.1).

Table 13.1 Worldwide prevalence of Rheumatoid arthritis (RA) (Li et al., 2012).

				Prevalence (%)		
Country	**Publication date**	**Age (Years)**	**Number**	**Males**	**Females**	**Total**
Asia						
China (our data)		≥16	10,550	0.08[a]	0.46[a]	0.28[a]
Vietnam (18)	2003	≥16	2119	0.10	0.44	0.28
Indonesia (19)	1993	≥15	5754	0.11	0.26	0.20
Philippine (20)	1991	≥15	846	0.2	0.2	0.24
Pakistan (21)	1998	≥15	1997	0.30	0.81	0.55
Japan (3)	1996	–	3150	0.11[a]	0.24[a]	0.17[a]
Thailand (22)	1998	≥15	2455	0	0.23	0.12
Kuwait (23)	2004	≥15	7670	–	–	0.04
South Europe						
France (24)	2001	≥18	9395	0.09[a]	0.51[a]	0.31[a]
Spain (25)	2002	≥20	2192	0.2	0.8	0.5
Italy (26)	1998	≥16	3294	0.13	0.51	0.33
Greece (27)	2006	≥19	8740	0.3	1.0	0.68
Yugoslavia (28)	1998	≥16	2184	0.09	0.29	0.18
Turkey (29)	2000	≥16	3173	0.07	0.67	0.38
North Europe						
Norway (30)	2000	≥20	110,215	0.27	0.58	0.43
UK (2)	2002	≥16	6593	0.44[a]	1.16[a]	0.81[a]
Finland (31)	1993	≥16	13,300	0.61	1.0	0.80
Sweden (32)	2011	≥15	–	0.43	1.11	0.77
South America						
Argentina (33)	2002	≥16	352,089	0.06	0.32	0.2
North America						
USA (34)	1999	≥35	1878	0.74[a]	1.37[a]	1.07[a]
Cuba (35)	2009	≥15	3155	0.4	1.7	1.2
Mexico (36)	2011	≥18	19,213	0.85	2.09	1.6

From Li, R., Sun, J., Ren, L. M., Wang, H. Y., Liu, W. H., Zhang, X. W., Chen, S., Mu, R., He, J., Zhao, Y., Long, L., Liu, Y. Y., Liu, X., Lu, X. L., Li, Y. H., Wang, S. Y., Pan, S. S., Li, C., Wang, H. Y., & Li, Z. G. (2012). Epidemiology of eight common rheumatic diseases in China: A large-scale cross-sectional survey in Beijing. Rheumatology, 51(4), 721–729. https://doi.org/10.1093/rheumatology/ker370.

Autoimmune pathology if unchecked can cause severe impairments, malformations, and/or loss of organ function. Autoimmune disorders place a significant economic, psychological, and social cost on society due to their chronic nature. Therefore, the care of patients with autoimmunity depends on the use of efficient, safe therapeutic drugs and a treatment plan.

The remaining section of this chapter will mostly cover RA and its experimental models, with some examples of other autoimmune diseases, where needed. RA affects people all over the world, with geographical differences in prevalence (Rudan et al., 2015; Abdel-Nasser et al., 1997; Alamanos & Drosos, 2005). Significant advancements in RA therapy have been accomplished during the past 20 years. Nonsteroidal antiinflammatory medicines (NSAIDs), corticosteroids, and disease-modifying antirheumatic drugs (DMARDs), such as methotrexate, sulfasalazine, and leflunomide, are among the allopathic (conventionally prescribed) therapies used to treat RA (Finckh et al., 2009; Muller et al., 2015; Her & Kavanaugh, 2015). This armament against RA recently gained the biologic DMARDs (drugs that target cytokines and cytokine receptors) (Fig. 13.1).

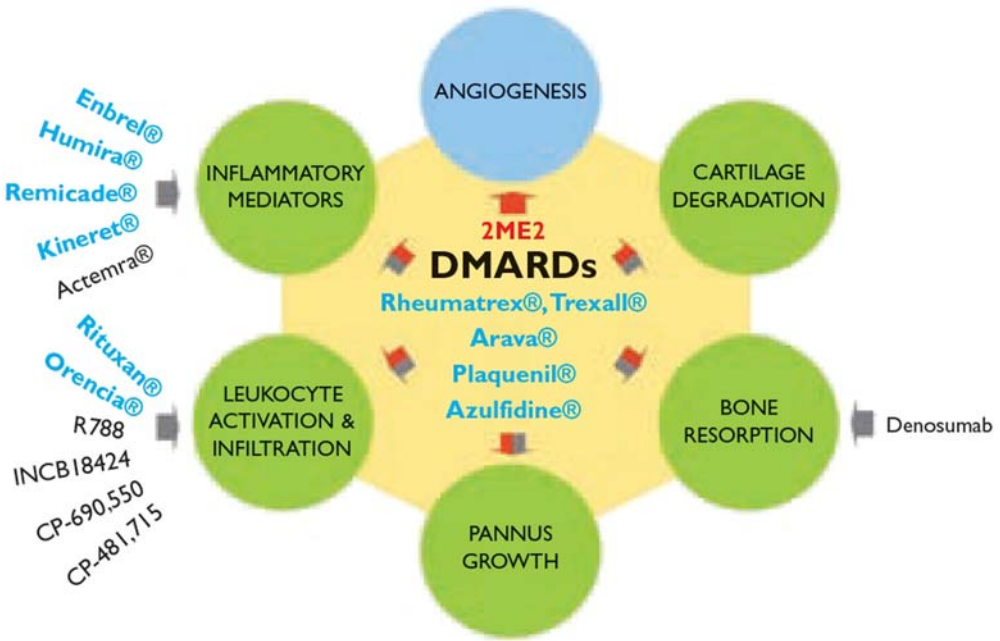

Fig. 13.1 Illustrates how the pathobiology of RA may be thought of as a disease made up of six different but connected processes (Fogler, 2008). Pathobiology of RA. *(From Fogler, W. E. (2008). Treating Rheumatoid Arthritis with Disease-Modifying Antirheumatic Drugs (DMARDs) and Biologics.)*

The biologics work by binding to a particular cytokine—such as tumor necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6) or interleukin-7 (IL-17)—and neutralizing its effects, or to a cytokine receptor—such as the TNF-alpha receptor—and preventing the binding of the endogenous cytokine ligand to its cognate receptor. Biologics are therefore highly powerful and effective at preventing the onset of RA. However, chronic use of these is linked to serious adverse responses, such as dangerous infections. Furthermore, many patients in developing nations find it extremely difficult to afford these common medications, especially biologics. Consequently, there is still a need for effective yet reasonably priced alternatives to current RA treatment options. Natural plant products are an essential and fruitful source for finding novel RA treatment drugs that fit these requirements. Many bioactive compounds with therapeutic potential have been found in plant products, and many of these eventually become drugs that are used to treat a variety of conditions, such as cancer, infectious diseases, and inflammatory and autoimmune diseases (Akerele, 1993; Amirghofran, 2012; Kolasinski, 2012; Aggarwal et al., 2013; Khan & Mukhtar, 2013; Basnvat and Kolasinski, 2014; Furst & Zundorf, 2015). Additionally, a variety of herbal treatments from traditional medical systems are either being used by people with autoimmune diseases, such as RA, with or without the knowledge of their primary care provider, or are being studied for their potential as therapeutics (Akerele, 1993; Amirghofran, 2012; Basnyat & Kolasinski, 2014; Chang et al., 2013; Furst & Zundorf, 2015; Kolasinski, 2012). These medicinal plants are employed in several traditional medical practices, such as traditional Chinese medicine (TCM), traditional Japanese medicine (Kampo), traditional Egyptian and other African medicine, and traditional Indian Ayurvedic medicine. Adjuvant-induced arthritis (AA) is a well-known experimental model of human RA (Tong & Moudgil, 2007; Venkatesha et al., 2011). The AA model has been extensively utilized to study the pathophysiology of autoimmune arthritis, screen prospective antiarthritic substances, and define the mechanisms of action of such substances. Subcutaneous immunization with heat-killed Mycobacterium TB H37Ra can cause AA in Lewis rats (RT.1l) (Mtb). All paws are affected by the sickness, which takes between 10 and 12 days to appear. However, the condition often has a more severe impact on the hind paws than the front paws. The degree of clinical arthritis can be semiquantitatively rated on a scale from 0 (no illness) to 4 (severe arthritis) based on the erythema and swelling of the paws, which are extensively documented elsewhere (Tong & Moudgil, 2007; Venkatesha et al., 2011). This ranking is helpful in determining the degree to which natural therapies can reduce the severity of arthritis. Some researchers have taken a different approach and used plethysmograph equipment to measure the size of the expanded paws.

A typical autoimmune condition known as rheumatoid arthritis (RA) is linked to progressive disability, systemic complications, early death, and socioeconomic expenses (Firestein, 2005, pp. 996–1042). Data Monitor estimates that 1.8 million Americans

suffer from RA, which has no identified cause. Aging is not a factor that is connected to RA. RA is a condition that develops when the immune system of the body misbehaves and attacks healthy tissue, resulting in inflammation, which then causes pain and swelling in the joints and may finally result in irreversible joint damage and excruciating incapacity. Progressive immobility and discomfort are the predominant signs and symptoms of RA, especially in the morning. Long-term sufferers will continue to experience joint degeneration for the rest of their lives. For RA, there is no known cure. Following a diagnosis, a course of treatment is suggested to reduce symptoms and/or halt or decrease the disease's progression. RA is linked to a significant economic, health, and disability impact on society. Due to the tendency of RA to be progressive in nature, including a worsening of symptoms over time, and commonly beginning during the early or middle years of life for many people, the illness frequently has a long-term impact on functioning (over 30 years for many people). This entails a huge social and economic cost (Kobelt, 2009). Many patients' abilities to do daily activities are significantly hampered by the chronic pain and exhaustion brought on by RA. Therefore, RA may reduce a person's ability to work. One research found that after 10 years of getting a diagnosis, up to one-third of RA patients are compelled to quit their occupations. The entire cost of the sickness is therefore significantly influenced by missed productivity. Due to the severe physical problems associated with RA, the illness is also expensive financially and can significantly lower quality of life (Emery et al., 2008). Thanks to improvements in RA diagnosis and treatment, the toll that the illness has on functioning and quality of life can now be reduced. It is important to keep in mind that many studies that examine the consequences of RA were conducted before there had been substantial recent improvements in therapy and do not take into account the potential for the most recent medicines to improve functioning. Many RA patients who, just a few decades ago, would have lost the ability to work and take care of themselves may now do so and lead full lives thanks to more advanced treatments.

The expense of medical care for RA is fairly considerable. According to estimates from the American College of Rheumatology, RA causes nine million medical visits and a quarter of a million hospital admissions per year in the US. In the US, the average yearly cost of care for a patient with RA consists of roughly $6000 in direct RA-related costs (excluding pharmaceutical prices) and an additional $2500 in nonRA-related costs. Hospital admissions account for 50% of all RA medical expenses (Yelin & Wanke, 1999). The expense of healthcare rises in direct proportion to the degree of RA disability. In one research, patients with a score of 3 (which indicates a high level of impairment) also incurred nearly 3 times the expense of health services compared to patients with a score of 1, which indicates a lesser level of disability (Fries, 1999). This statistic emphasizes the importance of proactive therapy to prevent or postpone the impairment that might be caused by RA. Because it can significantly restrict a person's ability to carry out job-related tasks, RA can be financially draining. In certain

circumstances, RA could even force a person to change employment or cut back on their work hours in order to make accommodations for their disability. A person may occasionally need to fully cease working due to a major disease. Each of these scenarios leads to financial loss over the course of a lifetime. According to one research, patients with RA usually have job challenges early in the course of the disease, and within 2 years after diagnosis, the use of disability benefits considerably increases (Gueskens et al., 2007). Another study that looked at the financial impact of RA and osteoarthritis patients found that individuals with RA had considerably greater expenses than those without the illness for home care, child care, the use of medical equipment and gadgets, and home remodeling. Additionally, RA patients had a substantially higher financial burden than osteoarthritis patients and were three times as likely to have had a decline in household income. Compared to patients with osteoarthritis, individuals with RA experienced a bigger reduction in work hours and a higher probability of losing their employment or retiring early. Additionally, compared to people with osteoarthritis and people without either illness, RA patients in the research had a substantially greater rate of unemployment owing to their condition (Gabriel et al., 2003).

2. Genetic factors

Genes account for almost 50% of the chance of having RA (Barton & Worthington, 2009). About 60% of RA patients in the United States carry a shared epitope of the human leukocyte antigen (HLA)-DR4 cluster, which is one of the peptide-binding sites of particular HLA-DR molecules associated with RA (e.g., HLA-DR beta *0401, 0404, or 0405). The HLA-DR1 (HLA-DR *0101) also carries this shared epitope and confers risk, especially in women. Other HLA-DR4 molecules, including HLA-DR beta *0402, do not carry the risk since they lack this epitope. The DNA of families with RA has been sequenced, and the results show that several resistance and susceptibility genes, including PTPN22 and TRAF5, are present (Potter et al., 2007). Involved genes include those not found in the major histocompatibility complex (MHC). Arthritis that begins before the age of 16 and lasts for more than 6 weeks is a defining feature of JIA and has an unknown origin. It is recognized to have genetically complicated features, and numerous genes are critical for illness development and symptoms (Prakken et al., 2011). Both the IL2RA/CD25 gene and the VTCN1 gene have been connected to JIA susceptibility loci (Hinks et al., 2009). According to some researchers, the future of treatment and comprehension of epigenetics and imprinting may be the basis for RA. According to Ahlmen et al. (2010), women are substantially more likely than men to have RA, which shows that parental genomic imprinting contributes to the development of the condition (Zhou et al., 2007). Imprinting is defined as the differential expression of maternal versus paternal genes caused by the parent of origin's distinct methylation of chromosomes. The study of epigenetics focuses on DNA expression changes rather than structural

changes in the DNA, such as those brought on by environmental methylation. Obviously, environmental influences in conjunction with immunological genetics will be the main focus of the investigation.

3. Infectious agents

Numerous infectious pathogens, including as Mycoplasma species (Hoffman et al., 2005), Epstein–Barr virus (EBV), and rubella virus18, have been proposed as probable causes of RA for many years. The following information serves as indirect support for this assertion:

Rare accounts of illnesses with flu-like symptoms occurring before the onset of arthritis, the ability of various bacteria or bacterial compounds to induce arthritis in laboratory animals (e.g., streptococcal cell walls), the presence of bacterial RNA and other products in the joints of patients. The action of many substances with antimicrobial properties as therapeutics for treating diseases (e.g., gold salts, antimalarial agents and minocycline). Additionally, emerging data suggests a connection between periodontopathic bacteria and RA. For instance, Porphyromonas gingivalis and other oral anaerobic bacterial antibodies typical to periodontal infection have been detected in significant concentrations in the synovial fluid of RA patients (Hitchon et al., 2010; Routsias et al., 2011).

4. Pathogenesis

RA is characterized by local inflammation that affects small and medium-sized joints in addition to systemic inflammation. The overall disease entity is clinically and pathobiologically heterogeneous in RA due to the varying activation of many autoimmune and inflammatory processes. The traits that various RA subgroups share, such as autoimmunity and inflammation, are important topics of research (Kerola, 2015).

4.1 Synovial immunologic processes and inflammation

Synovitis results from leukocyte infiltration of the synovial compartment. Leukocyte accumulation mostly indicates migration as opposed to local proliferation. The production of adhesion molecules such as integrins, selectins, and members of the immunoglobulin superfamily, as well as chemokines, is encouraged by endothelial activity in synovial microvessels, which aids cell mobility. Thus, neoangiogenesis, which is induced by local hypoxic conditions and cytokines, and insufficient lymphangiogenesis, which limits cellular outflow, are characteristics of both early and established synovitis (Polzer et al., 2008; Szekanecz et al., 2008). These microenvironmental changes, considerable synovial architectural reconfiguration, and local fibroblast activation all contribute to the build-up of synovial inflammatory tissue in rheumatoid arthritis.

4.2 Adaptive immune pathways

The genetics of rheumatoid arthritis and the presence of autoantibodies conclusively show that adaptive immunity is at the center of early pathogenesis. T lymphocytes are widespread in the synovial environment, although their functional significance is still poorly known. Cyclosporine or T-cell-depleting therapies have demonstrated little to no efficacy when directly targeting T cells (Panayi, 2006). This study raises the possibility of "wide spectrum" elimination of both regulatory and effector T cells and points to the requirement for T-cell subset targeting. Myeloid cells and plasma cytoid dendritic cells, which produce cytokines, HLA class II molecules, and costimulatory molecules necessary for T-cell activation and antigen presentation in rheumatoid arthritis, are prevalent in the synovium (Lebre et al., 2008; Mcinnes and Schett, 2007; Schroder et al., 1996). By blocking T-cell costimulation (through the interaction of CD28 with CD80 or CD86), abatacept, a fusion protein consisting of the FC region of IgG1 and the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), also works to impede antigen presentation (Fig. 13.2) effectively treats rheumatoid arthritis. T cells that are known to be auto-reactive against citrullinated self-proteins exist. Synovial T-cell oligoclonality, germinal-center responses, and B-cell hypermutation are examples of evidence of ongoing local antigen-specific, T-cell-mediated B-cell assistance, according to Cantaert et al. (2009) and Humby et al. (2009). Type 17 helper T cells (Th17), a subgroup of T cells that release interleukin-17A, 17F, and tumor necrosis factor (TNF-), are gaining more and more attention despite the fact that type 1 helper T cells are commonly believed to have a role in the pathogenesis of Rheumatoid Arthritis (RA) (Chabaud et al., 1998; Miossec et al., 2009). The balance of T-cell homeostasis is shifted toward inflammation by transforming growth factor, interleukin-1, 6, 21, and 23, which are generated by dendritic cells and macrophages and promote Th17 development while decreasing regulatory T cell differentiation. Interleukin-17A, which works with TNF- to promote the activation of fibroblasts and chondrocytes, is the subject of ongoing clinical studies. Forkhead box P3 [Foxp3+] regulatory T cells have been discovered in the tissues of rheumatoid arthritis patients, although these cells appear to have a constrained functional potential (Behrens et al., 2007). The presence of local TNF-α, which reduces the function of regulatory T cells, may potentially contribute to this imbalance between Th17 cells and regulatory T cells (Nadkarni et al., 2007). Another harmful mechanism is the activation of macrophages and fibroblasts through antigen-nonspecific, T-cell contact-mediated pathways. These pathways involve interactions between CD40 and CD40 ligand, CD200 and CD200 ligand, intracellular adhesion molecule 1, and leukocyte-function-associated antigen 118. Humoral adaptive immunity is a major factor in the development of rheumatoid arthritis. In fact, the production of molecules including a proliferation-inducing

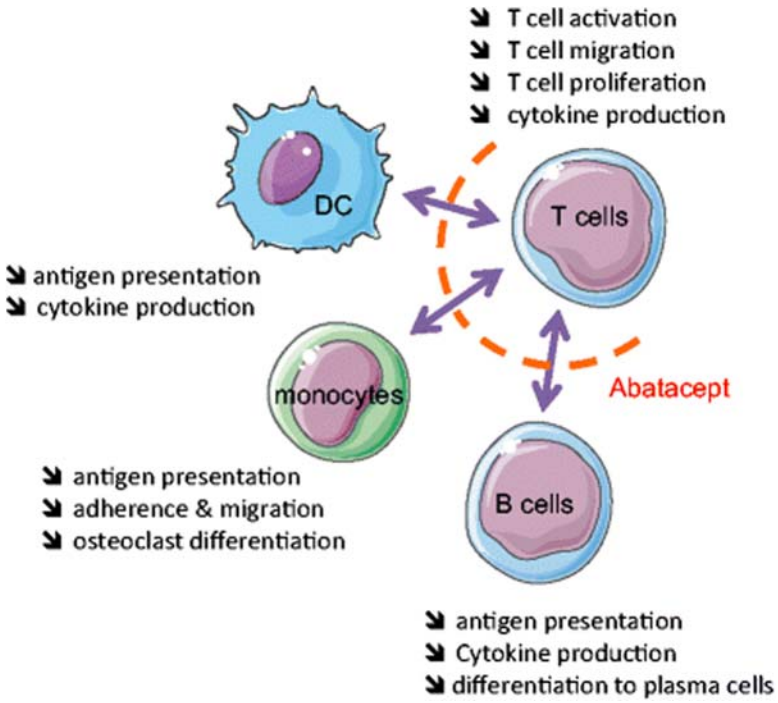

Fig. 13.2 Abatacept prevents $CD4^+$ T cell activation by interfering with the costimulatory signal CD28/CD80 and CD28/CD86. Abatacept is also capable of promoting immunosuppressive action on antigen-presenting cells such dendritic cells (DC), monocytes, and B cells in addition to CD4/CD28+ T cells (Gazeau et al., 2017). $CD4^+$ T cell activation by interfering with the costimulatory signal CD28/CD80 and CD28/CD86. *(From Gazeau, P., Alegria, G. C., Devauchelle-Pensec, V., Jamin, C., Lemerle, J., Bendaoud, B., Brooks, W. H., Saraux, A., Cornec, D., & Renaudineau, Y. (2017). Memory B cells and response to abatacept in rheumatoid arthritis.* Clinical Reviews in Allergy and Immunology, *53(2), 166–176. https://doi.org/10.1007/s12016-017-8603-x.)*

ligand (APRIL), a B-lymphocyte stimulator (BLyS), and CC and CXC chemokines support the development of ectopic lymphoid follicles in specific organs (Seyler et al., 2005). T-cell-B-cell aggregates are where most synovial B cells are found (e.g., CXC chemokine ligand 14 and CC chemokine ligand 21). In the synovium and juxta-articular bone marrow, plasmablasts and plasma cells can be detected in higher numbers. Rituximab's success in treating rheumatoid arthritis suggests that $CD20^+$ B cells have a negative role (Edwards et al., 2004). These clinical data indicate that the function of B lymphocytes and their offspring in the pathogenesis of rheumatoid arthritis extends beyond the creation of autoantibodies to also include the presentation of autoantigens and the production of cytokines (e.g., interleukin-6, TNF, and lymphotoxin-a). AntiCD20 antibodies do not specifically target plasma cells, and autoantibody levels might change following therapy.

4.3 Blood tests

Routine serologic testing for viruses neither significantly helps patients with early RA diagnose their condition with RA nor serves as a possible indicator of disease progression (Varache et al., 2011). There are three types of potentially helpful laboratory tests for RA suspicion: hematologic parameters, immunologic parameters, and indicators of inflammation.

These are included, along with the following.

- Levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)
- complete blood count (CBC)
- Rheumatoid factor (RF) assay Antinuclear antibody testing (ANA)
- Anticyclic citrullinated peptide (antiCCP) and antimutated citrullinated vimentin (antiMCV) tests are presently used in the 2010 American College of Rheumatology [ACR]/European League against Rheumatism [EULAR] classification criteria.
- Antibodies against filaggrin (AFA)
- MicroRNA (miRNA)

4.4 Hematologic parameters

4.4.1 Complete blood count (CBC)

As part of a complete blood count, your red and white blood cells, platelets, indicators of liver and kidney function, uric acid, and other numbers of cells and chemicals in your blood will all be analyzed (CBC). In RA patients, anemia (lower hemoglobin or red blood cells) and thrombocytopenia (lower platelets) are frequent CBC abnormalities (Venables & Maini, 2013).

4.5 Immunologic parameters

Immunologic markers include autoantibodies such RF, anticitrullinated protein antibodies (ACPA), antimutated citrullinated vimentin antibodies (MCV) antibodies, antifilaggrin antibodies (AFA), and microRNA (miRNA).

5. Rheumatoid factor (RF)

Over the course of their illness, 60%–80% of RA patients have rheumatoid factor, an immunoglobulin (Ig) M antibody that targets the Fc (crystallizable fraction) part of IgG, whereas less than 40% of individuals with early RA do not (Nell et al., 2005). Blood RF levels range from 3% to 5% in healthy individuals, and from 10% to 30% in aged individuals (Nijenhius et al., 2004). RF is a more well-established biomarker for RA than antiCCP because it was approved as one of the American College of Rheumatology's (ACR) diagnostic criteria for RA in 1987 (Arnett et al., 1988). The European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT) does not recommend RF as a diagnostic marker for RA (Combe et al., 2007), most likely at least in

part because of its low specificity, despite the fact that it is one of several prognostic markers used to identify patients with persistent and/or erosive disease. RF is a fairly nonspecific indication of RA because to its frequency in autoimmune, viral, and malignant diseases (Aletaha et al., 2010). Over 40% of RA patients have ANAs, despite the fact that tests for antibodies to the bulk of nuclear antigen subsets are negative.

5.1 Treatment

As soon as RA has been detected and a preliminary evaluation has been finished, treatment should begin. Recent guidelines (Deighton et al., 2009; Saag et al., 2008) address the therapy of RA, although patient preference is just as important. Women who are pregnant or planning a pregnancy should take extraprecautions due to the harmful impact that some medicines have on the developing fetus. Goals of therapy include minimizing joint pain and swelling, preventing deformity (such as ulnar deviation) and radiographic damage (such as erosions), maintaining quality of life (personal and work), and controlling extraarticular manifestations (Wasserman, 2011).

5.2 Mortality

Mortality rates among RA patients are higher than those in the general population. About 3–10 years' worth of life expectancy reduction has occurred (Mong et al., 2020). The excess mortality associated with RA has not changed over the last two to 3 decades. The excess mortality associated with RA has remained unchanged over the last two to 3 decades. In addition, recent studies show that RA patients have not experienced the survival gains seen in the general population, so that the gap between the two has widened (Gonzalez et al., 2007). The primary causes of mortality in RA patients include cardiovascular, infectious, hematological, gastrointestinal, and pulmonary issues. Positive treatment outcomes can imply a more promising future. A2005 Mayo Clinic research found that, regardless of other risk factors such as diabetes, alcohol abuse, high cholesterol, blood pressure, and body mass index, persons with RA had a two-fold increased chance of getting heart disease. Although the cause of this increased risk is not yet identified, chronic inflammation has been proposed as a potential contributing factor. The use of novel biologic drug therapy is anticipated to lengthen the lives of RA patients and reduce their risk of atherosclerosis development and progression. Despite being based on cohort and registry research; this is still entirely hypothetical. It is currently unclear if biologics improve vascular function in RA. The levels of HDLc and total cholesterol increased, while the atherogenic index stayed the same (Atzeni et al., 2010).

5.3 Natural products from plants against rheumatoid arthritis

Since ancient times, natural plant compounds have been remarkably effective in treating and preventing a variety of ailments (Grindlay & Reynolds, 1986; Kong et al., 2003; Phillipson, 2001).

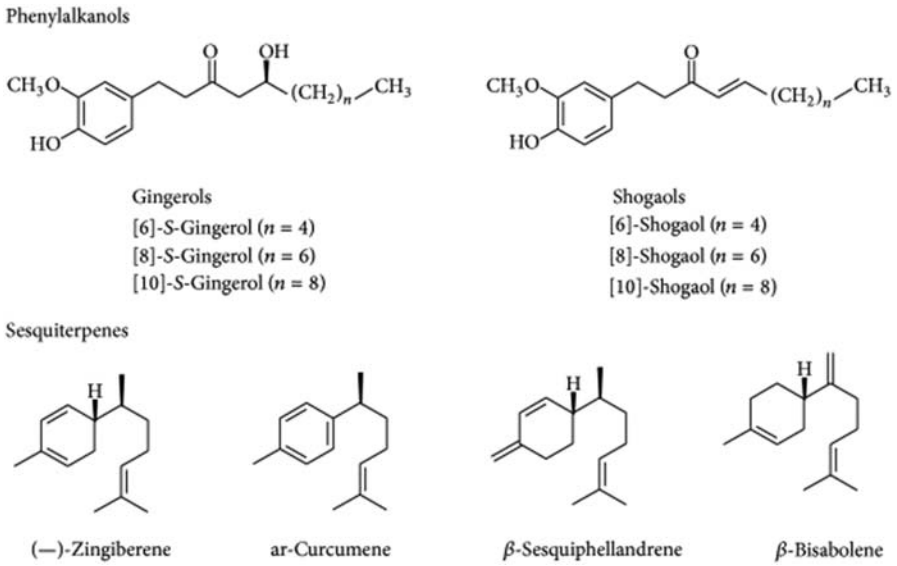

Fig. 13.3 Chemical structures of components of *Zingiber officinale* (Roufogalis, 2014). Chemical structures of components of ginger.

According to a World Health Organization (WHO) survey, out of the world's total population 80% are using traditional medicines (WHO, 2002). In USA, nearly 121 drugs are prescribed today, where 90 of the coma from the natural sources particularly from plants in a direct or indirect manner (Pathan, 2020). Herbal medicines can serve as an alternative source for treating RA symptoms in patients as well as addressing the problems with current allopathic drug-based therapy regimens. It is undeniable from a scientific perspective that *Zingiber officinale* Roscoe (from ginger family) plays a crucial part in reducing the excruciating pain and swelling connected with RA (Mascolo et al., 1989; Mustafa and Srvastava, 1990). Ginger is made from rhizomes of *Zingiber officinale* (Fig. 13.3).

The plant belongs to the Zingiberaceae family. Since the dawn of time, it has been extensively utilized as a spice and medicinal herb (Combe et al., 2007). Since *Zingiber officinale* includes phytochemical components and functions effectively as a medicinal agent, it has been playing significant roles in the battle against a variety of illnesses like asthma, diabetes, stroke, constipation, and others (White, 2007). According to reports, 100,000 t of ginger are produced each year, with China producing 80% of this amount (Kumar and Saxena, 2013).

5.3.1 *Zingiber officinale's beneficial effects on arthritis-related symptoms*

Since ancient times, *Zingiber officinale* (ginger) has been cultivated in China and other countries throughout the world as a source of medicinal plant for its usage as a spice

and for its therapeutic powers (Altman & Marcussen, 2001). There is a proof that consuming ginger may help lessen joint discomfort brought on by rheumatoid arthritis. The earliest scientific proof of ginger's capacity to decrease inflammation was provided by Kiuchi et al. (1982). Four new compounds were isolated from ginger, and all of them have the ability to inhibit the synthesis of prostaglandins, which is crucial for inflammation. It was shown in a 1992 follow-up study that ginger has antiinflammatory qualities via inhibiting the production of leukotrienes and prostaglandins. Efficacy against 5-lipoxygenase was demonstrated by a catechol-group-containing diarylheptanoid, which also reduced the production of leukotriene, a substance with antiinflammatory characteristics. Another constituent, namely, Yakuchinone A, inhibited prostaglandin production, which can again result in an antiinflammatory effect. In rats, Thomson and his team investigated the antiinflammatory effects of *Zingiber officinale* (Thomson et al., 2002; Ubaid et al., 2016; Hameed et al., 2016; Mohammad & Imad, 2013; Hameed, 2016; Hameed et al., 2015). Experimental rats were given an aqueous extract of *Zingiber officinale* orally or intravenously for a period of 4 weeks. Although ginger did not significantly lower prostaglandin E2 levels at low doses, it did so significantly at high doses. Consequently, ginger may reduce inflammation associated with RA. *Aloe barbadensis* is grown in several regions of India, including the north-west Himalayan region, as well as in Europe.

5.3.2 Aloe vera

Aloe vera has been one of the most important plants used in traditional medicine. Anthracene, cinnamic acid, anthranilic acid, and anthraquinone are all present in the Aloe vera plants that give it its action. A range of skin conditions, including minor wounds, insect stings, bruises, poison ivy, and eczema, can be treated using *aloe vera*. Additionally, it has uses as a purgative, antiinflammatory, diuretic, uterine tonic, spermatogenic, blood purifier, and fever reducer. It also possesses antibacterial and antifungal qualities. *Aloe vera's* antiarthritis properties are a result of the chemical anthraquinone. *Aloe vera* is a potent antiinflammatory and immune system stimulant. *Aloe vera* extract used topically reduces inflammation and arthritis in Sprague Dawley rats with adjuvant-induced arthritis (Altaee et al., 2017a, 2017b; Hussein et al., 2017). *Ashwagandha,* commonly referred to as Indian ginseng, is a significant old plant. The roots of *ashwagandha* have been used in Ayurveda and Unani, two traditional medical systems in India. It grows in arid areas of the subtropical states of Madhya Pradesh, Gujarat, Maharashtra, Rajasthan, Punjab, Haryana, and Uttar Pradesh. Alkaloids and steroidal lactones are thought to be responsible for the root's pharmacological effect. The most common alkaloids include withanine, pseudowithanine, tropine, real tropine, somniferine, and somnine. Two acyl glucosides from roots, called Sitoindoside-7 and Sitoindoside-8, have been identified. This plant has a long history of usage as an aphrodisiac, liver tonic, and antiinflammatory in addition to treating conditions including asthma, ulcers,

insomnia, and senile dementia. Clinical studies and animal studies support the use of ashwagandha for Parkinson's disease, inflammation, neurological issues, and anxiety. The consumption of *ashwagandha* may stop or slow the development of cancers in people. For a variety of health issues like aging, anemia, arthritis, weariness, sports fitness, and stress problems, it aids in delivering progressive, long-lasting improvements. Oral administration of *Withenia somnifera* Linn. root powder showed antiarthritic effects in rats given an adjuvant-induced arthritic condition (Kadhim, 2016; Al-yaseri et al., 2016). In South India, black pepper is both native to and grown there. Additionally, it is grown in Malaysia, Sri Lanka, Indonesia, and Brazil. India ranks first in the cultivation of this drug. Pipper contains an alkaloid piperine, volatile oil, pungent resins, piperidine and starch. It is used as an aromatic, stimulant, stomachic and carminative. It increases the secretion of gastric juices. It also increases the bio-availability of certain drugs. Piperine isolated from black pepper. In patients with carrageenan-induced acute paw arthritis, piperine given orally at doses of 20 and 100 mg/kg/day for 8 days reduced arthritic symptoms (Davis, 1986; Ubaid et al., 2017). Atype of flowering plant called *Cissampelo spareira* is a good source of Alkaloids, saponins, and moderate amounts of flavonoids. It has shown various beneficial properties such as hepatoprotection, antiseptic, antibacterial, antiinflammatory, antihistamine, antioxidant, diuretic, hypotensive, muscle relaxant, uterine relaxant, antihemorrhagic, cardiotonic, diaphoretic, expectorant, and antispasmodic. The leaves are applied topically to treat inflammation. The roots' ethanolic extract can be used to treat arthritis, diarrhea, and discomfort. The *Cissampelo spareira* root ethanolic extract showed a significantly protective action in a dose-dependent manner against fully developed arthritis caused by Freund's adjuvant (Joshph & Raj, 2010; Devis et al., 1986; Patwardhan et al., 2010).

5.3.3 Lappa Arctium (Asteraceae)

Various *Arctium* species have been employed in conventional medicine to treat inflammatory diseases of the skin and the body as well as chronic inflammatory bowel disease and rheumatoid illnesses. One of the primary components of *Arctium lappa* seeds is the lignan complex arctigenin. Macrophages produce nitric oxide and proinflammatory cytokines as RA progresses (NO). A few of the interleukins that arctigenin and its glycoside, arctiin, inhibit in order to have antiinflammatory effects are IL-1β, IL-6, IL-4, IL-5, and TNFα. Additionally, this natural chemical reduces NO levels by preventing the activity and production of inducible NO synthase (iNOS). The molecular processes behind the antiarthritic and antiinflammatory actions of arctigenin are hypothesized to include the nuclear signaling pathway (NF-kB) and phosphorylation of mitogen-activated protein kinases (MAPKs). A key molecular target, MAPK, promotes the development of inflammatory mediators, which are essential to the pathogenesis of RA. The intracellular signaling mechanism that produces TNF-α or IL-1β depends on the a-isoform. Additionally, it regulates COX-2 expression, an enzyme that regulates PGE2 under

inflammatory circumstances (Mirjalili et al., 2009). Inhibitors of MAPK such as arctigenin block the production of TNFa and IL-1β in monocytes and in synovial tissue of arthritic animalsIL-1β (Amresh et al., 2007; Bang et al., 2009; Singh et al., 2010). In an animal model of carrageenan-induced paw edema, the leaf of Arctium minus (Hill) Bernh. can also lessen inflammation (Arya et al., 2011).

5.3.4 *Artemisia absinthium L. (Asteraceae)*

In traditional Persian medicine, the erial part of *A. absinthium* is one of the ancient drugs that possess medicinal effects on neuralgia, rheumatoid disorder, as well as inflammatory diseases. Scoparone, one of the main active constituents of A. capillaris Thunb., suppresses inflammatory cascade produced by macrophages significantly in IFN-gamma and LPS-stimulated RAW 264.7 cell mediated by reducing the release of NO and PGE2 (Tripathy et al., 2010). Any decrease in NO concentration results from the inhibition of iNOS expression. The reduction of inflammatory response mediators is also greatly aided by scoparone's suppression of COX-2 synthesis (Kim, 2004). In RA-related circumstances, the nuclear signaling system controls COX-2 expression and the synthesis of cytokines such TNF-a, IL-1β, IL-6, and IL-8 (Fig. 13.4).

The erial parts of Artemisia sylvatica Maxim and Artemisia douglasiana Besser, which suppress the nuclear signaling pathway (NF-kB NF-jB), are mostly responsible for the decrease in RA symptoms (Combe et al., 2007; Nijenhius et al., 2004). According to phytochemical investigations, a variety of chemical components are assumed to be in charge of Artemisia spp antiarthritis and antiinflammatory activities. Artemisolide, 3-methoxytanapartholide, deacetyllaurenobiolide, moxartenolide, arteminolides, dehydroleucodine, scopoletin, scopolin, and esculetin are a few of them (Zhao, 2009).

One of the most significant traditional treatments for RA clinical symptoms is *Cassia angustifolia.* The effectiveness of this species in treating rheumatoid illnesses is not supported by scientific research. RA symptoms such as edoema and cartilage degeneration are improved by *Cassia alata* leaf, and leukocyte infiltration into the synovial fluid of rat knee joints is inhibited (Hameed et al., 2017; Lewis & Levy, 2011). Worldwide, citrus medica, sometimes referred to as the citron, is farmed. The peel, leaves, and root have long been used in traditional medicine in Asia, notably in India and Iran. In traditional medicine, this herbal remedy is suggested as a treatment for rheumatism, hepatitis, and arthritis. Antiinflammatory and antioxidant activities of the fruits have been demonstrated. The peels of *C. medica* and fruits of *C. unshiu* (Swingle) Marcow.

6. Medicinal plants as immunosuppressive agents

Cannabis calms the overactive immune system by acting on cannabinoid receptors including cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2). While

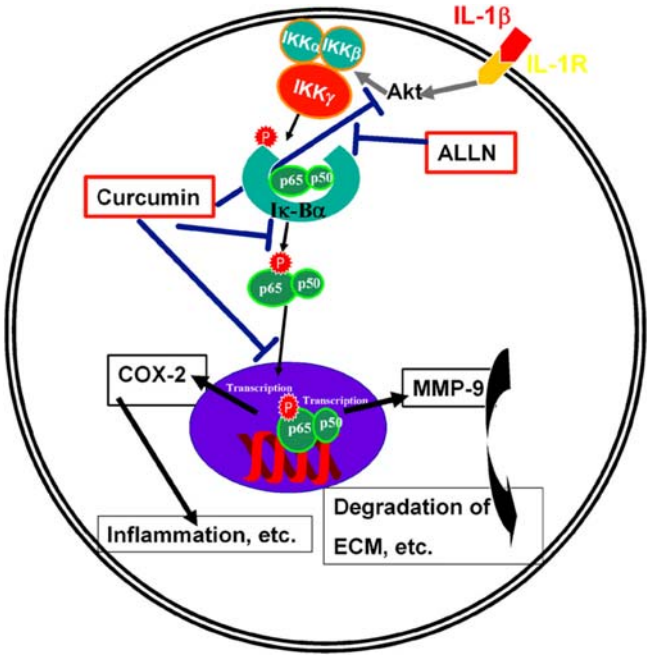

Fig. 13.4 Shows a working model of how curcumin inhibits the signal transduction that IL-1β and TNF-a cause in chondrocytes. When IL-1β binds to its receptor, IKKg kinase is activated, and Akt then phosphorylates IkBa, the cytoplasmic inhibitor of the NF-kB (p65/p50) complex. IkBa separates from the complex, freeing NF-kB to go to the nucleus and control the transcription of its target genes. Numerous proinflammatory genes, including MMP-9 and COX-2, are up-regulated by NF-kB. In addition, NF-kB causes the down-regulation of important signaling and matrix proteins in chondrocytes, including collagen type II and b1-integrin. Due to curcumin's ability to block IkBa degradation, NFkB activation and nuclear translocation are prevented. Its pharmacological effects block cytokine-induced NF-kB activation and proinflammatory enzyme activity in chondrocytes (Shakibaei et al., 2007). Curcumin inhibits the signal transduction that IL-1β and TNF-a cause in chondrocytes. *(From Shakibaei, M., John, T., Schulze-Tanzil, G., Lehmann, I., & Mobasheri, A. (2007). Suppression of NF-κB activation by curcumin leads to inhibition of expression of cyclo-oxygenase-2 and matrix metalloproteinase-9 in human articular chondrocytes: Implications for the treatment of osteoarthritis. Biochemical Pharmacology, 73(9), 1434–1445. https://doi.org/10.1016/j.bcp.2007.01.005.)*

CB2 receptors are prevalent in immune cells, CB1 receptors are mostly found in the brain. As a result, cancer and inflammatory diseases are treated with cannabis (Venkatesh et al., 2010) (Fig. 13.5 Structure 1).

Nocardia brasiliensis IFM0406 cultivated broth yields brasilicardin-A, which has immunosuppressive properties. It has the perhydro-phenanthrene moiety and amino acid active chemical components, together with the sugar rhamnose (Takeo et al., 2006) (Fig. 13.5 Structure 2).

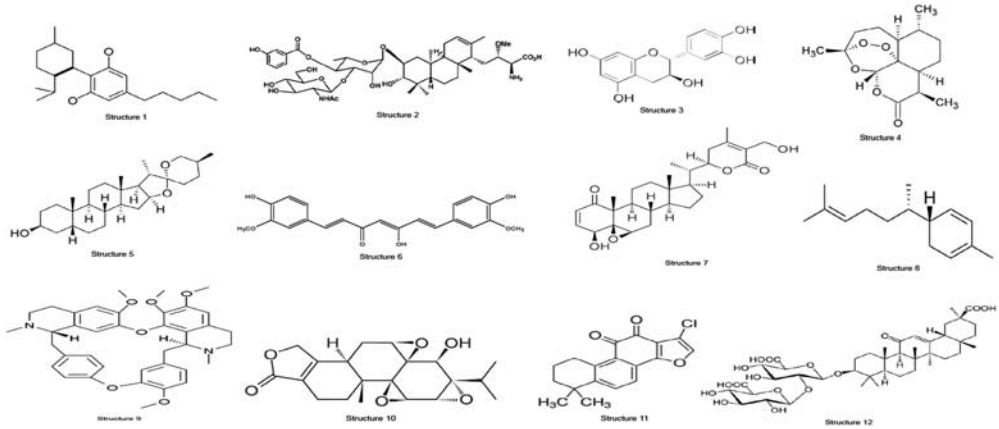

Fig. 13.5 Structures of some medicinally important phytocompounds. Phytocompound structure.

The dried leaves of the family *Camellia sinensis* are used to make green tea. Green tea contains a polyphenolic component called catechin that has antiinflammatory properties (Lorenzo & Munekata, 2016) (Fig. 13.5 Structure 3).

Systemic lupus erythematosus, rheumatoid arthritis, and other autoimmune illnesses have all been successfully treated using *Artemisia annua*. Artemesinin and its derivatives, artesunate and artemether, have immune-modulating effects, claim Lifei and Haochu (2016) (Fig. 13.5, Structure 4).

Sarsaparilla plant contains steroids such as sarsasapogenin, smilagenin, sitosterol, stigmasterol and saponins like sarsasaponin, smilasaponin. Sarsaparilla is beneficial for the treatment arthritis due to its ability to inhibit TNF-α induced NFk-β activation (Cullingworth, 1906) (Fig. 13.5, Structure 5).

The Zingiberace family member turmeric (*Curcuma longa*) is frequently used to treat inflammatory and infectious illnesses. The rhizome of the *Curcuma longa* plant contains the yellow pigment known as curcumin. According to (Jurenka, 2009), this Curcuma component controls immune function through cellular and humoral mediated immunity (Fig. 13.5, Structure 6).

Ashwagandha is frequently used to treat illnesses including psoriasis, arthritis, and rheumatism (*Withaniasomnifera*). The chemical makeup of Ashwagandha includes saponins (sitoindoside VII and VIII), steroidal lactones (withanolides, withaferins), and alkaloids (isopelletierineanaferine). In hyper-immune situations, these components, according to (Vetvicka & Vetvickova, 2011), have an immunosuppressive impact on B and T cell activity (Fig. 13.5, Structure 7).

Zingiber officinale, also known as ginger, is used to treat arthritic pain. In order to lessen pain and inflammation, the chemical zingiberene predominantly inhibits the

cyclooxygenase (COX) and lipoxygenase (LOX) pathways (Srivastava & Mustafa, 1989) (Structure 8, Fig. 13.5).

Stephania tetrandra is used for the treatment of autoimmune disease and rheumatic arthritis. The chemical ingredient, tetrandrine, inhibits TNF-α to generate immune-modulating effects (Lai, 2002) (Fig. 13.5, Structure 9).

It is generally known that Tripterygium wilfordii can cure autoimmune diseases including systemic lupus erythematosus and rheumatoid arthritis. Triptolide, its active ingredient, has antiinflammatory and immunosuppressive characteristics via inhibiting T-cells (Wilasrusmee et al., 2002) (Structure 10, Fig. 13.5).

The Labiatae family plant *Salvia miltiorrhiza* is used to treat immune system diseases. Tanshione IIA is the primary active component of Salvia miltiorrhiza (TSN). TSN works by decreasing proinflammatory cytokines such TNF-α, IL-2, and IL-4 (Metalidis & Kuypers, 2011) (Fig. 13.5, Structure 11).

Liquorice, or *Glycyrrhiza glabra*, is a member of the Fabaceae family and has immune-modulating qualities. The active ingredients that exert antiinflammatory actions by inhibiting calcineurin activity and T-cell proliferation include glycyrrhizin and glycyhrritinic acid (Regazzi et al., 2005) (Fig. 13.5, Structure 12).

Tanacetum parthenium, an Asteraceae plant, contains parthenolide, a significant sesquiterpene lactone that is used to treat rheumatoid arthritis. It inhibits the release of proinflammatory mediators such as nitric oxide, prostaglandin (PG) E2 and TNF-α (Allison, 2000) (Fig. 13.6, Structure 13).

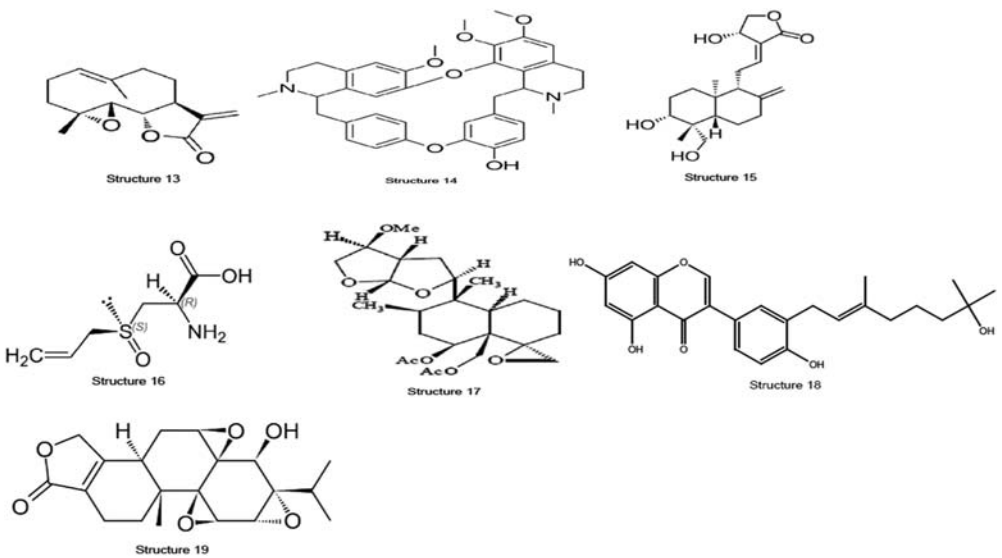

Fig. 13.6 Structures of some medicinally important phytocompounds. Phytocompound structure.

Berberis vulgaris, a member of the Berberidaceae family, suppresses the immune system. The active ingredient, berbamine, selectively inhibits STAT-4 expression and IFN-γproduction in cells (Gabardi et al., 2011; Setty & Sigal, 2005) (Fig. 13.6, Structure 14). The Acanthaceae plant *Andrographis paniculata* is advised for the treatment of rheumatoid arthritis. Andrographolide is the major component of *Andrographis paniculata*. According to (Akbar, 2011) and Burgos et al. (2009), It produces inhibitory effects on NF-κB transactivation activity (Fig. 13.6, Structure 15).

Alliin is chemically a sulfoxide which is the natural constituent of garlic (Allium sativum). It is an amino acid derivative of cysteine. By inducing an antiinflammatory gene expression, alliin can block LPS inflammatory signals and prevented the increase (Hodge et al., 2002) (Fig. 13.6, Structure 16).

The active component of Clerodendron trichotomum Tunberg Leaves (CTL), clerodinin-A, inhibits NF-kappa-B activation to stop the expression of proinflammatory genes in LPS-stimulated RAW 264.7 macrophages (Structure 17 in Fig. 13.6).

The geranylated flavonoids from Campylotropi shirtella roots (5,7,4′-trihydroxy-3'-[7-hydroxy- 3,7-dimethyl-2(E)-octenyl)isoflavone) have immunosuppressive effects (Shou et al., 2009) (Structure 18 in Fig. 13.6).

Triptolide is an active ingredient found in the Chinese plant Tripterygium wilfordii hook (TwHF). Chemically, it is a diterpenetriepoxide, which has potent immunosuppressive and antiinflammatory properties (Samira & Reginald, 2016) (Structure 19 in Fig. 13.6).

The immunosuppressive effects of medicinal plants that grow in different parts of the world are the subject of several investigations (Amirghofran, 2010). The plants that are being looked at for their immunosuppressive properties are shown in Table 13.2.

7. Multiple sclerosis

Multiple sclerosis (MS) is the most common nontraumatic disabling disorder that affects young people (Kobelt et al., 2017). The incidence and prevalence of MS, whose underlying cause is yet unclear, are rising in both industrialized and developing countries (Browne et al., 2014). A variety of recognized environmental variables, including vitamin D or ultraviolet B light (UVB) exposure, Epstein—Barr virus (EBV) infection, obesity, and smoking, as well as several genes all contribute to the complexity of the condition known as multiple sclerosis (Ascherio, 2013). It has long been recognized that multiple sclerosis is an organ-specific T-cell mediated autoimmune disease. However, the conventional T-cell autoimmune dogma is called into question by the efficacy of B-cell targeted treatments (Greenfield & Hauser, 2018). Relapsing remitting illness is assumed to be caused by early inflammation, whereas secondary and primary progressive MS are thought to be caused by delayed neurodegeneration (Coles et al., 2006; Leray et al.,

Table 13.2 List of Medicinal plants as immunosuppressive agents.

Name of plants	Family	Immunosuppressive effects
Argyrolobium roseum	*Papionaceae*	Decreased T cell and B cell numbers.
Andrographis poniculoto	*Acanthaceae*	Relief from rheumatoid arthritis symptoms.
Bupleurum folcotum	*Umbelliferae*	Inhibits the proliferation and activation of T cells.
Clerodendron trichotomum	*Verbenaceae*	Inhibits arachidonic acid release and prostaglandin E2 production
Compylotropis hirtella	*Leguminosa*	Inhibits mitogen induced splenocyte proliferation.
Drococepholum kotschyi	*Labiatae*	Inhibits lymphocyte proliferation.
Glyc:yrrhizo globro	*Fabaceae*	Inhibition of calcineurin activity and T cell proliferation.
Periploca sepium	*ASclepiadaceae*	Suppresses l-17production.
Periploca sepium	*Labiatae*	Inhibits IL-2 production.

From Sahoo, B. M., & Banik, B. K. (2018). Medicinal plants: Source for immunosuppressive agents. *Immunology: Current Research*, 2(1), 1–5. (Original work published 2018).

2010). Due to the discovery of increasingly strong biological medicines and an aggressive treatment plan, particularly treating to a target of no evident disease activity (NEDA), the long-term prognosis for MS patients is changing (pwMS). Some MS patients may be cured with more severe immune reconstitution therapy that cause a portion of patients to go into long-term remission (Murarao et al., 2017). People with more advanced MS have hope that recent successful studies of disease-modifying treatments would decrease the disease's progression while preserving their remaining function (Montalban et al., 2017). The conventional two-stage picture of Multiple Sclerosis' natural history is severely challenged by the fact that medicines seem to be effective at various points during the disease's progression (Giovannoni et al., 2017). Some of the studies related to treatment of MS by using medicinal plants is enlisted in Table 13.3.

8. Diabetes

Diabetes is the largest public health problem of the 21st century and a hidden epidemic (Larijani & Forozandeh, 2003). Diabetes is a chronic disease that gradually damages several organs in the body. After a few years have passed after the illness's initial onset, symptoms begin to manifest. During this time, major and permanent issues develop (Powers, 2007) Diabetes is a manageable condition, but if it is not managed, other illnesses, particularly cardiovascular issues, are more likely to develop. This occurs because the majority of diabetic patients also have additional health issues such obesity, hypertension, hyperlipidemia, and poor levels of physical activity, all of which have a significant impact on the development of cardiovascular illnesses. It is generally accepted that those who have both diabetes and hypertension have a twofold increased risk of developing cardiovascular illnesses. In diabetics, hyperlipidemia is a prevalent illness that is mostly

Table 13.3 Study of different medicinal plants on multiple sclerosis.

Plant	Author (Country)	Design of study	Dosage	Number	Duration of study	Effects
Ginkgo biloba	Johnson et al. (USA)		240 mg/day of ginkgo extract	22 MS patients	4 weeks	Treatment with ginkgo extract relieved fatigue with no adverse effect in MS patients.
	Lovera et al. (USA)		240 mg/day of ginkgo extract	38 MS patients	12 weeks	Improvement of the cognitive performance was reported in treated group.
	Brochet et al. (France)		240 and 360 mg/day of ginkgolide B	104 MS patients	1 week	Ginkgolide B was not an effective treatment for exacerbations of MS.
Zingiber officinale	Jafarzadeh et al. (Iran)	EAE model of MS in mice	200 and 300 mg/kg ginger extract	24	4 weeks	Ginger extract ameliorated EAE severity and modulated the expression of IL-27, IL-33.
Curcuma longa	Xie et al. (Japan)	EAE model of MS in rats	100 and 200 mg/kg curcumin extract	21	2 weeks	Curcumin decreased the inflammation and severity of EAE.
	Natarajan and Bright (USA)	EAE model of MS in SJL/J mice	50 and 100 μg curcumin in 25 μL DMSO	—	4 weeks	Curcumin decreased CNS inflammation and demyelination, also decreased the severity of EAE
	Mohajeri et al. (Iran)	EAE model of MS in rats	12.5 mg/kg of curcumin	20	17 days	Treatment with polymerized nano-curcumin decreased the severity of EAE and increased the remyelination.
Oenothera biennis	Firouzi et al. (Iran)	Double blind, randomized clinical trial	18–21 g/day evening primrose oil and *C. sativa* oils	100 MS patients	24 weeks	Treatment with cosupplemented *C. sativa* and evening primrose oils decreased the clinical score in MS patients.

Continued

Table 13.3 Study of different medicinal plants on multiple sclerosis.—cont'd

Plant	Author (Country)	Design of study	Dosage	Number	Duration of study	Effects
	Horrobin (Canada)	Double blind, randomized clinical trial	–	14 MS patients	24 weeks	Treatment with colchicine and evening primrose oil improved manual dexterity test and clinical score in MS patients.
Hypericum perforatum	Naziroglu et al. (Turkey)	In-Vitro studies on neutrophils of MS patients	20 μM/mL *H. perforatum* for 2 h.	9 MS patients	–	Treatment with *H. perforatum* indicated the protective effects on oxidative stress in MS patients.
Vaccinium macrocarpon	Gallien et al. (France)	Double blind, clinical trial placebo controlled	36 mg/day Cranberry extract (proanthocyanidins)	171 MS patients	1 year	Treatment with cranberry extract versus placebo did not prevent UTI occurrence in MS patients.
Nigella sativa	Fahmy et al. (Egypt)	EAE model of MS in rats	2.8 g/kg *Nigella sativa* extract	22	4 weeks	N. sativa ameliorated the clinical signs of EAE, suppressed inflammation and enhanced remyelination in the CNS.
	Noor et al. (Egypt)	EAE model of MS in rats	2.8 g/kg *Nigella sativa* extract	22	4 weeks	N. sativa suppressed inflammation in EAE rats. Also, it enhanced remyelination in cerebellum and reduced the expression of TGF-β1.

associated with coronary heart disease that manifests too soon. Hyperlipidemia also causes an increase in insulin resistance. Additionally, obesity is a significant risk factor for heart disorders due to its link to insulin resistance. More importantly, a risk factor for both insulin resistance and cardiovascular disease is physical inactivity. Exercise and weight loss have been shown to decrease blood pressure, prevent type 2 diabetes, and reduce the risk of cardiovascular diseases (Laligani et al., 2005). About 90%–95% of all instances of diabetes are type 2, making it the most prevalent type. In recent decades, type 2 diabetes has become much more common everywhere. Many type-2 diabetes patients are unaware of their condition because it is a silent illness. They become aware of their predicament as the illness progresses and its effects, such as kidney and eye impairment, become more obvious (Ghaed et al., 2012; Baharvand-Ahmadi et al., 2016). According to the interview data, 24 species of medicinal plants from 19 families are used to cure diabetes in Shiraz. The Compositae (13%), Rosaceae (13%) and Cucurbitaceae (8%), families have the most antidiabetic plants. Decoction was the most commonly recommended form (62%), while fruits were the plant components that were used the most (38%). Table 13.4 shows ethnomedical data regarding plants used to treat diabetes in Shiraz.

9. Systemic lupus erythematosus

Systemic lupus erythematosus, or SLE, is a multi-systemic, chronic autoimmune illness with intricate clinical manifestations. The male to female incidence ratio is 1:5 to 10, and the majority of them are discovered in young women (Dorner & Furie, 2019). According to earlier research, SLE may be influenced by environmental, endocrine, immunological, and genetic factors. The most widely used therapies for SLE in western medicine at the moment are nonsteroidal antiinflammatory drugs, antimalarial drugs, glucocorticoids, immunosuppressive drugs, plasma therapy, and systemic lymph node irradiation therapy (Wallace, 2015). The condition can currently only be momentarily controlled by these medications and techniques. The negative impacts of western medicine are also becoming more and more obvious at the same time.

Traditional Chinese Medicine (TCM) intervention therapy can effectively treat clinical symptoms while also minimizing the harmful effects and side effects of western medicine (Ma et al., 2016). By accumulating evidence, TCM has been demonstrated to be significant throughout both the acute and remission phases of SLE. TCM has been widely utilized to successfully treat SLE in recent years with excellent results. As its therapeutic benefit has continued to grow, medical practitioners and academics both locally and globally have begun to take note (Ma et al., 2016). Currently, the TCM treatment Lang Chuang Wan (LCW) is used widely in the treatment of SLE. LCW generally comprised of 16 herbs: *Lonicera japonica* Thunb (Jinyinhua, 53.6 g), *Forsythia suspensa* (Thunb.) Vahl (Lianqiao, 53.6 g), *Taraxacum mongolicum* Hand (Pugongying, 53.6 g), *Coptis chinensis* Franch (Huanglian, 13.4 g), *Rehjnannia glutinosa* Libosch (Dihuang,

Table 13.4 Lists the scientific name, common name, family name, the plant parts utilized, the manner of usage, and the medicinal properties of the plants that were gathered.

Scientific name	Family	Persian name	Useable part of plant	How to use	Traditional use in Shiraz
Juglans regia L	*Juglandaceae*	Gerdoo	Leaves	Oral	Diabetes
Cinnamomum verum	*Lauraceae*	Darchin	Bark	Leaves	Diabetes
Ficus johannis Boiss.	*Moraceae*	Anjir-Vahshi-Daraki	Leaves	Oral	Diabetes
Lamium amplexicaule L	*Lamiaceae*	Gazaneh Say	Aerial parts	Leaves	Diabetes
Trigonella monpeliaca L	*Papilionaceae*	Shanbalileh	Aerial parts	Decoction	Diabetes
Phaseolus vulgaris L	*Leguminosae*	Loobia	Aerial parts	Leaves	Diabetes
Arctium lappa	*Cornpositae*	Baba-adam	Aerial parts	Leaves	Diabetes
Urtica dioica L	*Urticaceae*	Gazaneh	Aerial parts	Leaves	Diabetes
Olea europaea	*Oleaceae*	Zeitoon	Leaves	Oral	Diabetes
Amygdalus scoparia Spach.	*Rosaceae*	Badam-Koohi-Arzhan	Leaves	Leaves	Diabetes
Salvia officinalls	*Labiatae*	Maryam-Goli	Aerial parts	Leaves	Diabetes
Anethun graveolens dhi	*Apiaceae*	Shevid	Leaves	Decoction	Diabetes
Achillea millefolium L	*Cornpositae*	Boomadaran-Sefid	Aerial parts	Decoction	Diabetes
Cotoneaster persica Pojark	*Rosaceae*	Shirkhesht	Aerial parts	Decoction	Diabetes
Lxillirion tataricum (Pall.)	*Amaryllidaccac*	Khiarak	Leaves	Decoction	Diabetes
Roem et Schult.	*Fabaceae*	Adas-almolk	Leaves and fruits	Decoction	Diabetes
Securigera securidaca	*Cucurbitaccae*	Hendavaneh-Aboojahl	Fruit	Fresh fruit decoction	Diabetes
Allium sativum	*Alliaceae*	Sir	Balb	Oral	Diabetes
Lagenaria vulgaris	*Cucurbibceae*	Kedoo	Fruit	Oral	Diabetes
Curcuma longa	*Zingibcraccae*	Zardchooveh	Bark	Leaves	Diabetes
Gundelia tournefortii	*Cornpositae*	Kangar	Leaves	Oral	Diabetes
Zataria multilflora	*Lamiceae*	Avishan-Shirazi	Leaves	Decoction	Diabetes
Berberis vulgaris	*Berberidaceae*	Zereshk	Fruit	Decoction	Diabetes
Mespilus germanica	*Rosacea*	Azgil	Fruit	Decoction	Diabetes

An examination of diabetes-related therapeutic herbs from an ethnomedical perspective (Baharvand-Ahmadi et al., 2016).
From Baharvand-Ahmadi, B., Bahmani, M., Naghdi, N., Saki, K., Baharvand-Ahmadi, S., & Rafieian-Kopaei, M. (2015). Review on phytochemistry, therapeutic and pharmacological effects of myrtus (Myrtus communis). Der Pharmacia Lettre, 7(11), 160–165. http://scholarsresearchlibrary.com/dpl-vol7-iss11/DPL-2015-7-11-160-165.pdf.

53.6 g), *Rheum officinale* Baill (Dahuang, 20.1 g), *Glycyrrhiza uralensis* Fisch (Gancao, 13.4 g), *Scolopendra subspinipes* Mutilans (Wugong, 2.42 g), *Paeonia ladi* flora (Chishao, 26.8 g), *Angelica sinensis* (Danggui, 13.4 g), *Salvia miltiorrhiza* Bge (Danshen, 13.4 g), *Scrophularia ningpoensis* Hemsl (Xuanshen, 53.6 g), *Prunus persica* Batsch (Taoren, 26.8 g), *Carthamus tinctorius* (Honghua, 20.1 g), *Cryptotympana pustulata* Fabricius (Chantui, 53.6 g), and *Fritillaria thunbergii* Miq (Zhebeimu, 26.8 g).

10. Graves' disease

Graves' disease (GD), an autoimmune disorder that only affects one organ, is characterized by hyperthyroidism, extensive goiter, and thyroid-related ophthalmopathy (Bahn et al., 2011). Hyperthyroidism of GD is due to the binding of thyrotropin receptor (TSHR) on thyroid cells by stimulatory autoantibodies, which act as a TSHR agonist and induce excessive secretion of thyroid hormones, causing the thyroid to escape the control of the pituitary gland (Ross et al., 2016). GD is the most frequent cause of hyperthyroidism, with 20−30 cases per 100,000 people per year in iodine-deficient regions (Kahaly et al., 2018). Female patients are reported to be more likely to develop GD, with a population prevalence of 1%−1.5% (Nystrom et al., 2013). Instead of encouraging apoptosis or preventing excessive thyrocyte proliferation, the main function of currently available medications for GD is to decrease the synthesis of thyroid hormones by reducing thyroid peroxidase expression (Cooper, 2005). Due to the ineffectiveness of these antithyroid medications untreating goiter, GD patients with large goiters experience significant financial hardship and mental stress. Potential treatments for GD goiter include proapoptotic and antiproliferative strategies.

With the widely application of bioinformatics, network pharmacology has emerged as effective tool toward TCM research (Hao & Xiao, 2014). Based on omics data analysis, high-performance virtual computing and network database retrieval, network pharmacology could not only build the priority of disease-associated genes, but also predict the target information and pharmacological effects of TCM compound systematically (Luo et al., 2020). It is believed to a new original discipline of cost-effective drug development in the era of artificial intelligence and Big Data (Li, 2021, pp. 148−154). In the current results, we adopted a network pharmacology approach coupled with molecular docking to screen the putative targets and signaling pathways of DNR against GD and then conducted experimental verification on a rat model of GD goiter to further illustrate the pharmacological mechanism of DNR against GD.

11. Conclusion

A number of medicinal plants have been used to treat various immunological issues. Numerous studies have been carried out to determine the mode of action of plant-based immunosuppressive drugs. The pharmacological properties can thus be expanded

to other immunosuppressive applications and subject to additional confirmatory study. Medicinal plants that contain immunosuppressive compounds include *Withania somnifera*, *Glycyrrhiza glabra, Andrographis paniculata, Salvia miltiorrhiza, Zingiber officinale, Berberis vulgaris, Curcuma longa*, and others. These plants' active components and immunosuppressive mechanisms have both been the subject of in-depth research. New therapeutic treatments for RA and other autoimmune diseases can be developed from plant-derived natural compounds, which is an important and promising resource. Herbal extracts are preferred by traditional medical practitioners, whether used alone or as a combination with numerous herbs. The pharmaceutical industry usually seeks out pure herbal components with bioactivity that replicates, if not exceeds, that of the parent herbal extract as part of its drug development process. In that situation, a surprising but not unexpected possibility is that the purified components may be both more poisonous and more potent than the complete natural extract. Carefully designed dosage studies that were followed by suitable product changes because of active industry-academia collaboration would be beneficial for expanding the use of natural products in the treatment of autoimmune and other illnesses. Collaboration between practitioners of complementary and alternative medicine and conventional (allopathic) medicine is necessary for the use of these items for the treatment of a variety of disorders (CAM). This is important to anticipate and manage unexpected interactions between conventional (allopathic) and complementary and alternative medicine (CAM) products used concurrently by patients with autoimmune diseases and other illnesses.

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DEVELOPMENTS IN IMMUNOLOGY SERIES

ROLE OF MEDICINAL PLANTS IN AUTOIMMUNE DISEASES

CONCEPTS, PERSPECTIVES, AND UTILIZATION

EDITED BY REETIKA MAHAJAN, FAHEEM SHEHJAR, SAJAD MAJEED ZARGAR, KHALID Z. MASOODI, ZAHOOR A SHAH

The immune system is a group of complex biological structures and processes in an organism that gives protection against a wide range of pathogenic organisms and simultaneously distinguishes these pathogens from an organism's own healthy cells and tissues, thus maintaining homeostasis in the body.

It has been an age-old practice to use extracts and other parts of various plants in treating many diseases. A number of plants contain various pharmacologically active substances that can be used to treat different diseases. Among these medicinal plants, many have shown good immunomodulatory properties and could act as natural immunosuppressant agents in treating autoimmune disorders.

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