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Review

A Review on Plant-Derived Immunomodulatory Agents: Hopes as an Alternative Medicine in the Management of Immune-Related Disorders

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Abstract

In humans, the immune system serves as a protective barrier against infection; however, when the immune system is out of balance, it can harm the host. Immunomodulators are chemicals or medications that have been employed in the clinic to treat an unbalanced immune response. The majority of immunological medicines in clinical use are cytotoxic. They harm the patient's quality of life by causing various side effects and being associated with higher production costs, longer lead times, and a high failure rate. Furthermore, obtaining single-compound chemicals with low toxicity, high efficacy, and selectivity for specified disorders is difficult for researchers. As a result, techniques based on alternative medicine are gaining attraction in drug development, focusing on innovative natural compounds utilized to treat various disorders. Many plant molecules founded to have biologically beneficial properties. This review aimed to look at the immunomodulatory activity of plant-derived chemicals from widely-used plants.

Keywords: Immune system; Immunomodulators; T cells; Cytokines; Tumor necrosis factor; Interferons; Humoral and cellular immunity

Introduction

The human body's natural resistance consists of a system of biological structures and processes that protect against any foreign invader. An efficient natural defense system must be able to counter any invading pathogen [1]. Immunity can also distinguish between the body's own proteins/cells and strange things. The immune response begins as soon as the foreign particle identifies. It is the collective and coordinated response of specific cells and mediators against unknown substances [1]. Previous infection, immunisation, and various environmental cues are all factors that trigger immunity. For example, some infections cause a rise in body temperature, also known as a fever. An increase in temperature can kill some microorganisms—the body's mending process triggered by fever [2]. The body's natural defense system has three primary lines of defense: innate (general) immunity, adaptive (specialized) immunity, and passive immunity.

Types of Immunity

Innate immunity

Innate immunity (non-specific immune system) acts as the primary defender against infection, responding within a minute. However, since this system does not

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retain any memory of the attack, the immunity is not long-lasting and non-specific to any particular foreign invaders [3]. The innate immune system comprises various components such as barriers, effector cells, antimicrobial peptides, soluble mediators, and cellular receptors.

Components of Innate Immunity

Barriers

Barriers are vital in keeping foreign invaders from reaching infection-prone organs. Cell walls of closely bound cells at the cellular level prevent invaders from penetrating deeper tissue. The external layer of the epidermis acts as a chemical shield as it contains keratinocytes present in a layer of extracellular matrix proteins, tightly linked to desmosomes and expressing pattern recognition receptors (PRRs). Keratinocytes also produce antimicrobial peptides and cytokines, which further destroy the microbes. Also, the genitourinary, digestive, and respiratory tract membranes contain epithelial cells that fight the invading pathogen to prevent them from penetrating the host. Moreover, the epithelial cells produce defensins and antimicrobial peptides that enhance the action of tumor necrosis factor-alpha (TNF-α) and inflammatory cytokines, including interleukin-1 (IL-1) [4].

Effector Cells

Effector cells are significant players in the natural defense mechanism of a host. These cells include phagocytic, natural killer, innate lymphoid, endothelial, and epithelial cells.

Phagocytic Cells

Phagocytic cells are composed of granulocytes, monocytes/macrophages, and dendritic cells. Phagocytic cells are involved in the early stage of infection and devour any foreign invaders to protect the body [5]. Phagocytic cells include a cluster of eosinophils, neutrophils, basophils, mast cells, monocytes, and dendritic cells that find, engulf, and destroy microbial pathogens through receptors.

Eosinophils, also known as eosinophiles, are a type of white blood cell (WBC) that helps the immune system fight infections. Eosinophils, mainly fight against parasites in helminthic infections, participate in allergic processes, regulate inflammation, maintain the function of the epithelial barrier, and affect tissue remodeling, besides serving as a bridge between innate and adaptive immunity [6].

Neutrophils have granules in their cytoplasm, which carry a range of toxic substances that destroy or arrest the growth of fungi and bacteria. Neutrophils are the first cells to arrive at the site of infection and are the most abundant type of phagocyte [7]. A typical adult bone marrow produces more than 100 billion neutrophils daily; there is a ten-fold increase in this number in case of acute inflammation [8].

Basophils have granules filled with histamine involved in allergic reactions. However, these cells are not phagocytic, i.e., when basophils encounter an antigen, they liberate histamine, which raises the blood flow to the damaged tissues, resulting in inflammation and swelling [9].

Lastly, mast cells are found in mucous membranes and connective tissues and help in wound healing, fighting against infections, and participating in allergic responses. When activated, these cells release granules rich in heparin and histamine and liberate chemokines and several other hormonal mediators [10].

Macrophages or monocytes are involved in the innate immune system; these cells participate in phagocytosis, antigen-presentation to T-cells, and lymphocyte activation. When macrophages are triggered, they release and also stimulate the release of cytokines. Moreover, they act as immune modulators, i.e., they produce cytotoxic factors against tumors associated with immunity [11]. Any bacteria binding to the surface receptors of macrophages is destroyed by engulfing or releasing reactive oxygen species (ROS).

Dendritic cells are phagocytic cells found in the skin and inner mucosal lining of the lungs, intestines, nose, and stomach, often exposed to the surrounding environment. These cells are considered antigen-presenting cells (APC) involved in the innate immune system. These APCs introduce antigens through major histocompatibility complex (MHC)-class II molecules and further activate the T cells [12].

Natural Killer (NK) Cells

Natural killer (NK) cells are large granular lymphocytes forming part of the innate immune system. They do not directly attack the foreign substance invaders but destroy the virus-infected and malignant host cells. NK cells recognize the infected cells by a process known as 'missing self,' which is seen in virus-infected or malignant host cells having abnormally low levels of the MHC-1 complex, a cell-surface marker. The receptors on the NK cells are known as inhibitory receptors. When the NK cells are activated, they secrete chemokines and growth factors, such as TNF-α, interferon-gamma (IFN-γ), and interleukins (IL-5, IL-10, and IL-13). The granules in the NK cells consist of perforins and granzymes, which induce lysis in the target cells. Furthermore, they also express PRRs such as Toll-like receptors (TLR-2, 3, 4, 5,7, and 8) [13-15].

Innate Lymphoid Cells (ILCs)

Innate lymphoid cells (ILCs) are one of the recently discovered elements of the natural immune system. They are found in the lymphoid and non-lymphoid

tissues but are seen rarely in peripheral blood. ILCs, mainly those on the mucosal surface, play a significant role in mucosal immunity and homeostasis [16]. NK cells, ILC1, ILC2, ILC3, and Lymphoid Tissue-inducer (LTi) are the five categories of ILCs. They are responsible for developing protective immunity in the lymphoid tissue and mucosal surfaces, remodeling, lymphoid organogenesis, and homeostasis in tissue stromal cells. This type of cell is associated with allergy and autoimmunity.

Endothelial Cells, and Epithelial Cells

The endothelial and epithelial cells contain surface PRRs which recognize the pathogen-associated molecular patterns (PAMPs) and release antimicrobial peptides and pro-inflammatory cytokines, including IL-1, IL-6, and IL-8. The alveolar epithelium is an essential defense against inhaled pathogens and is the most studied innate immunity component [17]. It consists of two types of cells – type I and type II, which play a significant role in about 95% of the alveolar epithelium covered by type 1 cells that express a receptor called TLR-4. Furthermore, in response to lipopolysaccharide (LPS) stimulation, they produce IL-6, TNF-α, and IL-1β. Alveolar type II cells produce cytokines and chemokines, such as TNF-α, IL-6, IL-1β, and monocyte chemoattractant protein-1 (MCP-1). Additionally, in response to bacterial and viral stimuli, the growth-related oncogene alpha (GRO-α) and granulocyte-macrophage colony-stimulating factor (GM-CSF) is produced.

Antimicrobial Peptides

Antimicrobial peptides (AMPs) are a ubiq*uitous com*ponent of defensive systems found in all living things. Their widespread distribution over the evolutionary scale underlines their effectiveness and importance in combatting infections. AMPs are quickly generated and available after illness, allowing them to quickly kill a wide range of pathogens. Almost all living species and cell types retain the potential to create AMPs [18].

Other Effector Microbicidal Mechanisms

ROS are crucial weapons against pathogenic bacteria and fungi in the antimicrobial defense arsenal of host immunity. Innate immune cells, such as macrophages and neutrophils, generate ROS as cytotoxic effectors that can irreversibly oxidize and damage pathogen cellular structures. ROS are vital intracellular mediators that induce proper antibacterial responses and tune the inflammatory response simultaneously [19].

Nitric oxide (NO) aids in the control of intracellular microbial pathogen multiplication or death [20].

Soluble Mediators

An extensive range of soluble mediators, such as chemokines, complement systems, and cytokines, have a role in innate immunity [21]. These mediators defend the body from pathogens in the early stages of illness and are crucial for averting potentially dangerous infections. The components of soluble mediators that have a substantial impact on the innate immune responses are,

Cytokines

Innate immune cells produce and release cytokines, which are essential responses to infection and inflammation in the body [22]. Some of them has discussed below,

TNF-α: The main trigger of the inflammatory response is TNF-α. It raises vascular permeability, giving rise to fluid accumulation and immunoglobulins, complement, and other blood proteins accumulating in the tissue. TNF-α ensures teamwork in the battle against illness [23].

IL-1: Monocytes, dendritic cells, macrophages, endothelial cells, and specific epithelial cells are the leading producers of IL-1. It also works co-actively with TNF to increase inflammation. The function of IL-1 stimulates the coagulation pathway, raise inflammation, activates the liver to produce acute-phase proteins, and catabolism of fat for energy transformation. And other parts include triggering fever and sleep, inducing the synthesis of collagen and enzymes for scar tissue formation, promoting the synthesis of adhesion factors on endothelial cells and leukocytes for diapedesis, and stimulating macrophages. Chemokines are a category of cytokine that allows leukocytes to migrate from the bloodstream to the tissues around an inflammatory site [24].

IFN-γ: Interferons control the activity of nearly every immune system component. IFN-γ can enhance macrophage activation, intervene in antiviral and antibacterial immunity, promote antigen presentation, and organize innate immune system stimulation. And also synchronize lymphocyte–endothelium interaction, controls Type 1 and 2 T helper (Th1/Th2) balance, and regulates cell proliferation and apoptosis. It has released by stimulated T cells and NK cells [25, 26].

Interferon-alpha (IFN-α): Involved with viral infection resistance [27].

IL-12: It activates the production of IFN-γ and TNF-α from NK cells and T cells and lowers IL-4 mediated suppression of IFN-γ [28].

IL-15: IL-15 is essential for the formation and survival of NK cells and the functional maturation of dendritic cells and macrophages [29].

IL-10: Is a cytokine with a wide range of functions in immunoregulation and inflammation [30].

Transforming growth factor-beta (TGF-β): TGF-β

regulates the magnitude and kind of immune responses to microorganisms and plays a critical role in immunological tolerance and homeostasis against self- and benign antigens in the steady-state [31,32].

Chemokines

Chemokines, also known as chemotactic cytokines, are short peptides (60 to 100 amino acids) that have linked to cytokines. Its primary purpose is to promote leukocyte migration. They are produced in response to specific signals, such as pro-inflammatory cytokines, and play a vital role in the recruitment of neutrophils, lymphocytes, and monocytes [33, 34].

Complement Systems

The complement system, commonly referred to as the complement cascade, is an immune system component that boosts (complements) antibodies and phagocytic cells' ability to eliminate pathogens and damaged cells from an organism, stimulate inflammation, and assault the pathogen's cell membrane. The complement system has made up of about 50 proteins and protein fragments, including seric proteins and cell membrane receptors.

Seric proteins: Complement is a chief element of the innate immune system that aids in the protection against all foreign diseases via opsonizing, chemotaxis, and activation of leukocytes, as well as cytolysis by the C5b-9 membrane attack complex [35]. Neutralization and microbial aggregation, complement activation, and control of inflammatory responses are all functions of collectins [36]. C-reactive protein (CRP) induces complement, binds to Fc receptors, and behaves as an opsonin for specific pathogens, similar to immunoglobulin (Ig)G [37]. Coagulation was a vital feature of the innate immune response during evolution—localization of infected or damaged tissue [38].

Cellular receptors: Toll-like receptors (TLRs) identify pathogen-associated molecular patterns originating from various microorganisms by playing an essential role in the innate immune system [39].

Nucleotide-binding domain, leucine-rich repeat-containing (NLRs) can detect cytoplasmic infections indicating that they are essential sensors for immune responses to intracellular bacteria [40].

C-type Lectin Receptors (CLRs) recognize bacterial and fungal sugar moieties [41].

The retinoic acid-inducible gene-I -like receptors (RLRs) detect viral or self-RNA in the cytoplasm, triggering an indication cascade involving type 1 IFN and downstream innate immunity genes, allowing the infection to be controlled [42].

Adaptive immunity

Adaptive immunity (specific or acquired immunity) is exclusive to a particular pathogen and long-lasting by evoking memory responses to pathogens encountered earlier. Adaptive immunity has classified into two components – cell-mediated immune response and humoral immune response [43]. The latter form of immune response comprises numerous reactions, including delayed-type hypersensitivity responses (DTH) and the production of cytotoxic cells [44]. An inflammatory response occurs 24 to 72 hours after the immune system detects an antigen as foreign. T cells, rather than antibodies, are involved in this sort of immunological response (which is made by B cells).

Humoral immune responses

Humoral immune responses are called antibody-mediated immunity and have mediated by B-cells. The B-lymphocytes develop in the bone marrow and are primarily involved in humoral immunity. When the B-cells encounter an antigen or foreign substance, they differentiate into plasma cells, which then secrete immunoglobulins [45]. The mature B cells in the bone marrow gain many surface receptors (membrane-bound protein complexes), which bind to specific antigens with the antibodies on their surface.

Cell-mediated immune response

This type of response has mediated by T-lymphocytes that develop in the bone marrow and mature in the thymus. The T-lymphocytes multiplying in the thymus will classify into helper T-cells, regulatory T (T-reg) cells, and cytotoxic T-cells. Once the T-lymphocytes have activated in the presence of an antigen, the helper T-cells secrete cytokines that further trigger the B-cell differentiation to produce antibodies. The T-reg cells control the immune response, while cytokines stimulate the cytotoxic T-cells to kill the infected cells. In cell-mediated immunity, T-cells release various cytokines, phagocytes, and antigen-specific cytotoxic T-lymphocytes in response to the antigen. This type of immune response is mainly involved in fighting infections and tumors. During the secondary condition, the T-lymphocytes recognize the antigen and release their proteins, i.e., lymphokines, which stimulate the macrophages to destroy the pathogen [46].

Passive Immunity

The transfer of antibodies to an unprotected individual for disease prevention or treatment is called passive immunity [47].

What happens when the Immune System does not work properly

The immune system of an individual can malfunction at times. Immuno deficits present at birth; immunosuppressive drugs, such as steroids; unneeded or hyperactive immune responses, such as allergies; or immune responses to one's own body, known as autoimmune

diseases. So let's look at a few and see how the immune system reacts in these unusual circumstances.

Immunodeficiency
Immunodeficiencies can cause by inherited or spontaneous genetic abnormalities, immune-suppressing medicines, or infections that harm immune system components.

Genetic variations
An alteration in a person's genes might cause the immune system to be deficient or non-functional. Most of these disorders are uncommon, but when they occur, they are frequently detected early in life due to a high number of infections. For example,
• SCID is a severe combined immunological deficit caused by issues with T cell development [48].
•DiGeorge syndrome is a kind of SCID that occurs when T cells do not mature properly.

Medications
Chemotherapies for cancer and immunosuppressive drugs for various rheumatologic and allergy illnesses are examples of medications.

Infections
An excellent example of a long-term immune system disorder caused by infection is the human immunodeficiency virus (HIV). The virus infects T cells, mainly CD4+ T cells, which are a kind of T cell. HIV causes two problems. First, the immune response that significantly hampered. The second issue is that, in fighting the infection, the immune system attacks one of its components. The CD4+ T cell count can help determine which stage of HIV infection a person has. CD4+ T cells drop early in the infection, known as the acute phase. The infected person may have influenza-like symptoms but is unaware of their disease. However, the virus can be discovered in high quantities in a person's blood if examined during the acute phase. The T cell population first recovers, only to decline over time. The person is usually asymptomatic during this time, which can be brief or prolonged. The CD4+ T cell population eventually depletes to the point where the individual becomes susceptible to additional illnesses is the start of the final stage, also known as acquired immune deficiency syndrome (AIDS) [49].

Overactive Immune Responses
When our immune system reacts to something that is not infectious, it can unintentionally generate disease symptoms. This type of immunological response that linked to allergic reactions. Similarly, our immune systems can sometimes overreact, overwhelming our bodies and leading to death.

Allergies and allergic reactions
Mast cells, a type of immune system cell, are most closely related to allergic reactions. Mast cells are plentiful beneath our skin and in the linings of our digestive, respiratory, and vaginal tracts. A substance called histamine is released when a mast cell triggers an allergic reaction. Histamine triggers inflammation, draws in white blood cells, and boosts mucus production and blood flow. Muscle contractions that induce coughing, sneezing, vomiting, and diarrhea are caused by mast cells that line the respiratory and digestive systems. Mast cells also rely on immunoglobulin E (IgE) or immunoglobulin G (IgG) antibody interactions to initiate an immune response [50]. When a mast cell is triggered, the type of antibody it is connected with determines the sort of allergic response it produces:

Cytokine storm
When our immune system reacts to a possible infection, it causes damage to normal tissues. The innate immune response is non-specific and fast-acting, resulting in tissue damage; whereas the adaptive immune system targets infected cells. Most of the time, the damage is minor, and other resistant response components attempt to "establish order" in the infected area even as the conflict continues [51]. Some bacteria may enter the bloodstream and infect other body parts if tissue damage is severe. Sepsis is a condition that occurs when an infection enters the bloodstream. As a result, immune reactions take place in conflicts all over the body. This attack, together with the immune response to it, can sometimes become overwhelming, resulting in a "cytokine storm." When this happens, the immune system effectively kills the body's ability to operate normally. A person's organs begin to fail, and medical treatment may or may not help reverse the situation.

Autoimmunity
Identifying a "foreign" intruder from one's cells and tissues is one of the most critical components of immunity; otherwise, our immune system would target our body. Autoimmune disease occurs when an organism's immunological homeostasis that disrupted, resulting in an aberrant response to its tissue. Self-reactive T cells, autoantibodies, and inflammation are all signs of autoimmunity. Celiac disease, type 1 diabetes, Addison's disease, and Graves' disease are all autoimmune disorders [1].

Treating Immune related problems
Immunomodulators are drugs used to treat immune-related problems that affect the immune system – they can act as immune stimulators or immune suppressors

or alter different aspects of the immune response.

Classification of Immunomodulators

Immunostimulators
An immune stimulator facilitates the immune response in an immunocompromised condition, such as a viral infection, cancer, or autoimmune disease.

Immunosuppressors
Immune suppressors suppress the body's natural resistance and control the immune response in case of tissue or organ transplant and autoimmune diseases like rheumatoid arthritis, Sjögren's syndrome [52], systemic lupus erythematosus, and Crohn's disease.

Immunoadjuvants
Immunoadjuvants are special immunostimulants used to enhance the efficacy of vaccines [53,54]. Adjuvants use to improve immunity in immunocompromised patients.

Drawbacks of immunomodulators
These immunomodulatory substances or drugs may raise the risk of infection by acting on the immune system. Conditions, including those caused by opportunistic agents, can be severe even if they are generally mild and risk-free. For example, reactivation of latent tuberculosis is also a known side effect, especially concerning the current generation of immunomodulatory medicines [55,56]. On the other hand, the disadvantages of immunomodulatory drugs include:
• High cost.
• Use of toxic chemicals.
• Risk of failure.
• Logistic and time concerns during the production of the drug.
• Limited success with us.
These factors make it challenging to identify a single compound that can target multiple diseases; therefore, there is an urgent need to produce such drugs with less investment, minimum failures, and those having shorter production time [57].

Methods for screening of immunomodulatory activity of plants
The standard screening procedure is to extract a single constituent or fraction from herbal plants and test its biological activity using traditional pharmaceutic methods. The entire animal model is the most common pharmacological screening model. It is crucial in medical evaluation since it appears to respond to medicines' efficacy, side effects, and toxicity. Several *in vitro*, *in vivo*, and *ex vivo* screening approaches for medicinal plants with immunomodulatory activity have been listed [58].

In vivo
The Latin phrase "*in vivo*" means "inside the alive." It refers to the tests, studies, and procedures carried out by researchers in or on a whole living creature, such as a person, laboratory animal, or plant [59]. Some *in vivo* screening approaches are phagocytic activity, total and differential leukocyte counts, DTH, neutrophil adhesion, nitroblue-tetrazolium reduction test, immunohistochemistry assays, haemagglutination antibody (HA) titer, splenocyte proliferation assay, macrophage function assay (NO production), carbon clearance and *Candida albicans* clearance, and lymphocyte phenotyping.

In vitro
In vitro means "in glass" in Latin. It refers to medical operations, tests, and experiments conducted outside of a living creature by researchers. An *in vitro* study occurs in a lab setting, such as a test tube or petri dish [59]. Some *in vivo* screening approaches are chemiluminescence, nitro-blue tetrazolium, nitrous oxide assays, real-time polymerase chain reaction (PCR) technique, western blot assay, enzyme-linked immunoassay (ELISA), 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay, plaque assay, and bead panel assay.

Plant Immunomodulators

Plant-derived compounds as immunomodulators
From ancient times plant-derived natural compounds have been used in the treatment protocols for different diseases, such as those induced by fungi, viruses, bacteria, or insects [60]. The therapeutic effects of plants are because of their indigenous natural compounds that exert their action similar to conventional allopathic drugs. Therefore, the recent focus of research has been the development of plant-derived natural compounds as potent and safe immune-altering drugs owing to their superiority in overcoming the shortcomings of conventional immunomodulatory drugs. The current study, in this regard, offers an overview of certain plant-derived natural chemicals and their potential involvement in both innate and adaptive immunity. Table 1 discusses the traditional applications of plants and the structure of their components.

Stereospermum chelonoides (L.f.) DC.
Stereospermum chelonoides (L.f.) DC. (Syn: *Stereospermum suaveolens* (Roxb.) DC) roots are used to treat inflammations, fevers, pain, asthma, blood diseases, and liver disorders, among other ailments. The root is used in ayurvedic formulations such as indukantam, dashmularishta, ghritam, dantyadyarista, and amritarishta [61]. The primary chemicals isolated in the root were N-triacontanol, dehydrotectanol,

dehydro—lapachone, and lapachol [62]. Based on the medicinal importance of roots, they were examined immunomodulation against non-specific immune responses using an *in vivo* assay including phagocytic activity, total and differential leukocyte counts, DTH, and neutrophil adhesion test, and nitroblue-tetrazolium reduction test in Swiss albino rats. Further, reverse-phase high-performance liquid chromatography (RP-HPLC) analysis of ethanolic *S. chelonoides* root extract revealed the presence of a natural phenolic compound named lapachol and its derivative dehydro-α-lapachone. *In vivo* assays of ethanolic *S. chelonoides* root extract at 300 mg/kg dose increased sheep red blood cells (SRBC) count. And induced DTH response, neutrophil adhesion, neutrophil index, nitroblue-tetrazolium reduction, and phagocytic activity [63]. Furthermore, oral administration of 300 mg/kg of *S. chelonoides* root extract significantly increased the total leukocyte cell count. Also, the population of monocytes and neutrophils observes a decrease in the population of lymphocytes, basophils, and eosinophils compared with the control group. *S. chelonoides* root extract containing the compound lapachol and its derivative dehydro-α-lapachone was thus confirmed to possess immunostimulatory activity through various *in vivo* assays [63].

Tinospora sinensis (Lour.) Merr.

Tinospora sinensis (Lour.) Merr. (Syn: *Tinospora cordifolia* (Willd.) Miers) is one of the essential herbs with proven immunomodulatory properties [64]. Furthermore, α-d-glucan, isolated from the plant's stem, has been demonstrated to boost the immune system [65,66]. Compounds from *T. sinensis* such as 11–hydroxymustakone, N-methyl-2-pyrrolidone N-formylannonain, cordifolioside A, magnoflorine, tinocordiside, syringin, N-methyl-2-pyrrolidone,11-hydroxymustakone were evaluated for their immunomodulatory activity. In these studies, the compounds syringin and cordifolioside A exhibited immunomodulatory activity. Moreover, at a concentration of 0.1–2.5 µg/mL, 11-hydroxymustakone, N-methyl-2-pyrrolidone, N-formylannonain, magnoflorine, and tinocordiside demonstrated a significant rise in nitric oxide, reactive oxygen species, and phagocytic activity *in vitro* [67].

Atractylodes lancea (Thunb) DC

In both *in vitro* and *in vivo* experiments, the crude extract of *A. lancea* and its bioactive compounds- eudesmol and atractylodin- have shown potential clinical value for cholangiocarcinoma (CCA) control [68]. The immunomodulatory activity of *A. lancea* and its bioactive chemicals in causing CCA cell death would support *A. lancea*'s role in CCA regulation [69,70]. Immunomodulatory properties of this plant, as well as several of its isolated components, have been demonstrated [71]. Therefore, based on earlier investigations, a randomized, double-blinded, placebo-controlled phase-I clinical trial was conducted to study the immunomodulatory activity of the compounds isolated from *A. lancea* [72]. These compounds include atractylodin and β-eudesmol.

Further, another study investigated the *in vitro* and *ex vivo* effects of crude extracts of *A. lancea* on human blood samples. In the *in vitro* evaluation, *A. lancea* extract inhibited both IL-6 and TNF-α expression in Concanavalin A-mediated inflammation in peripheral blood mononuclear cells at all concentrations. β-eudesmol inhibited only IL-6 expression at all concentrations. In contrast, atractylodin inhibited IL-6 at the highest concentration and both cytokines at the lowest concentration, as determined by the real-time polymerase chain reaction (PCR) technique. The *ex vivo* studies was conducted using blood samples from healthy humans. A single oral dose of 1000 mg of the standardized *A. lancea* extract in the form of a capsule increased the production of cytokines (TNF-α, IL-17A, IL-2, and IL-4) and decreased the production of IL-10 and IFN-γ when compared with placebo [72]. Additionally, 1000 mg of the standardized *A. lancea* extract as capsules significantly decreased the production of all cytokines and inhibited IL-17A production when given in multiple oral doses. Furthermore, the section increased lymphocyte subpopulations of B-lymphocytes, CD8+ cytotoxic T-lymphocytes, CD4+ T-helper lymphocytes, and NK cells.

Stevia rebaudiana (Bertoni) Bertoni

Stevioside is a diterpenoid glycoside with various pharmacological properties. Stevioside is helpful in liver damage due to antioxidant, anti-inflammatory, anticancer, and antidiabetic effects [73-77]. *In vivo* immunohistochemistry assays revealed that co-administration of the plant in thioacetamide-administered Wistar rats inhibited the structural and histologic changes of the liver and also increased both body weight and liver weight. Thioacetamide-administered rats had the lowest glycogen levels, and the stevioside co-administration partially prevented this reduction, thereby preserving liver functionality. Furthermore, chronic thioacetamide administration enhanced the protein levels and p65 mRNA; whereas stevioside co-administration lessened this effect, as inferred from qRT-PCR and western blot assay. In the *in vitro* studies, incubating co-cultured cells (hHSC/VL-17A cells) with LPS and ethanol resulted in increased levels of (NF)-κB mRNA, but the administration of stevioside prevented this increase. In silico assays demonstrated that stevioside had the lower binding energy for TNF-R1, i.e., −0.9 kcal/mol. With the TLR4-MD2 complex, the docks showed higher bind-

ing of −5.6 kcal/mol, which further activated the NF-κB pathway [78].

Phyllostachys bambusoides Siebold & Zucc.

Bamboo is a rich source of flavonoids and glycosides and a rich source of effective antioxidants [79]. The bioactive fraction (PBC) of *P. bambusoides* revealed the presence of flavones – orientin and iso-orientin [80]. The immunomodulatory activity of PBC was examined using *in vivo* assay models in BALB/c mice. PBC at 200 mg/Kg enhanced the DTH reaction, increased primary and secondary antibody titer, Con-A and LPS-stimulated splenocyte proliferation, and improved macrophage function. Moreover, it upregulated the production of nitric oxide, enhanced the production of TH1 (TNF-ɣ) and TH2 (IL-4) cytokines, and increased the expression of CD80 and CD86 in BALB/c mice [80].

Cassia fistula L.

C. fistula is one of the most well-known plants in the Vedas and Upanishads. *C. fistula* is used to cure a variety of disorders in the old Ayurveda system, including pruritus, vitiligo, diabetes, and blood vomiting [81-83]. The immunomodulatory activity of the plant is also reported in modern studies. The *in vitro* immunomodulatory activity of hot aqueous extract of the pods and leaves of *C. fistula* was evaluated in albino rats [84]. The study used the tube-agglutination test to report that the hot extracts of pods and leaves, when administered to healthy rats at oral doses of 125, 250, and 500 mg/kg, respectively, increased the antibody titers in the serum samples. HPLC analysis confirmed the presence of quercetin dihydrate in both the extracts and kempferol in the leaf extract. The effect of hot extract of pods and leaves on the cell-mediated immune system test using 1-chloro-2,4-dinitrobenzene-sensitized albino rats fed with 125 mg/kg body weight of hot extract of leaves and 250 mg/kg of hot extract of pods demonstrated an increase in skin thickness. These results indicate that both extracts induce the proliferation of B and T lymphocytes [84].

Tinospora crispa (L.) Hook. f. & Thomson

T. crispa extracts contain phenols and flavonoids, such as catechin, luteolin, murine, and rutin with high antioxidant properties [85]. These phenolic compounds and flavonoids are responsible for the high activity of antioxidants. Some studies indicate that T. crispa can be an essential source of nutrients and natural antioxidants [86]. T. crispa was investigated for its immunomodulatory activity and found to stimulate the proliferation of RAW264.7 cells in a dose-dependent manner, measured by the MTT assay. T. crispa extract and the active compounds, such as eicosenoic acid, cordioside, boldine, and quercetin detected in T. crispa by liquid chromatography-tandem mass spectrometry (LC-MS), were found to have resulted in an increased expression of IL-6 and IL-8 in RAW264.7 cells *in vitro* [87].

Polysaccharides with immunomodulatory activity

The following sections describe certain plant-derived polysaccharides and their possible role in innate and adaptive immunity. Table 2 lists traditional applications for plants.

Dendrobium catenatum Lindl.

Prior research indicates that the main active components of *Dendrobium* species are polysaccharides and bibenzyl [88-94]. Numerous studies revealed that polysaccharides mainly triggered the NF-kappa B and Janus Kinases/Signal Transducers and Activators of Transcription (JAK/STAT) signaling pathways, respectively [95-97]. The findings showed that upregulating NF-kB and ERK1/2 may be how DOP-1 induces immunological activity. A crude polysaccharide obtained from the ethanol, and aqueous extracts of the *D. catenatum* (Syn: *Dendrobium officinale* Kimura & Migo) stem, was examined for its modulation in the immune activity [98]. In splenocyte proliferation assay, all fractionated *D. catenatum* polysaccharides DOP, DOP-1, and DOP-2 at a 12.5–100 µg/mL concentration increased proliferation *in vitro*. A 3.125–50 µg/mL concentration enhanced NK-cell activation due to increased splenocyte proliferation in the NK cell. However, compared with other DOP-1 polysaccharides, at a 50 µg/mL concentration, they showed higher proliferation activity and NK cell activation. Furthermore, the polysaccharides augmented phagocytosis in RAW264.7 cells when used at 12.5–200 µg/mL. However, this assay found that DOP-1 possessed low phagocytic activity. And these polysaccharides increased the NO production dose-dependently by inducing macrophages. Here, DOP displayed a more excellent production of NO when compared with other polysaccharides. DOP-1 showed the highest production of IL-2 and IL-4 at a concentration of 50 µg/mL compared to the control group, as inferred from ELISA. Moreover, at 200 µg/mL, DOP-2 increased the production of IL-1β and TNF-α when compared with other polysaccharides. Based on these findings, DOP-1 and DOP-2 function as active immunomodulating agents [98].

Chlorophytum borivilianum Santapau & R.R.Fern.

Previously, the ethanol extract of *C. borivilianum* represented *in vivo* immunomodulatory activity [99]. The

polysaccharides extracted from the *C. borivilianum* roots using hot water also showed immunomodulatory activity, as illustrated by *in vitro* and *in vivo* models [100]. In the *in vitro* studies of NK cell activity, the *C. borivilianum* polysaccharide increased the activity of NK cells two-fold (98 ± 2.5%) when given at a concentration of 5 µg/mL; whereas at 25 µg/mL, the percentage increment was 58.4 ± 0.3, as estimated by flow cytometry. Based on the haemagglutination titers, *C. borivilianum* aqueous extract (100 µg/mL), *C. borivilianum* polysaccharide fraction (50 and 100 µg/mL) significantly increased the titer value in Wistar rats. In the *in vivo* model, the aqueous extract of *C. borivilianum* caused a notable increase in the IgG level, as measured by ELISA [100].

Eupatorium adenophorum Spreng.

Numerous bioactive substances extracted from E. adenophorum have demonstrated antibacterial and immunomodulatory activities [101]. Numerous plant polysaccharides have immunomodulatory characteristics and therapeutic promise. Concerning the H1N1 and H3N2 strains of influenza, several polysaccharides from the plant's *Portulaca oleracea* L., *Gracilaria lemaneiformis, Gyrodinium impudicum*, and Panax ginseng C.A.Mey. have been characterized as effective antiviral agents [102-106]. *E. adenophorum* polysaccharide increased the secretion of IFN-γ, IL-6, and TNF-α in RAW264.7 cells and A549 cells (as evaluated by qPCR) and in lungs of influenza virus (H5N1)-infected BALB/c mice (as assessed by ELISA a qPCR), respectively. Both *in vitro* and *in vivo* studies revealed its immunomodulatory a ctivity [107].

Clerodendrum splendens G.Don

The volatile oil of *C. splendens*, prepared by extraction of fresh flowers with n-hexane, was active against *Staphylococcus aureus* and *Candida albicans* [108]. *C. splendens* extracts also have antipyretic and anti-inflammatory effects [109]. The subfractions CSP-AU1 and CSP-NU1 induced NO, and cytokines, such as IL-1α, IL-1β, IL-6, IL-10, TNF, and granulocyte macrophage-colony stimulated factor (GM-CSF) in murine J774.A1 macrophages and human peripheral blood mononuclear cells. These subfractions also increased the serum levels of monocyte chemoattractant protein-1, TNF, IL-6, IL-10, macrophage inflammatory protein-1β/CCL4, and macrophage inflammatory protein-1α/CCL3. Furthermore, C57BL/6 mice with experimental autoimmune encephalomyelitis, when treated with CSP-AU1 at 50 mg/kg, showed a decrease in the severity of the disease. Besides, TNF, IL-13, IL-17, GM-CSF, and IFN-γ were reduced by increasing the transforming growth factor in the lymph node (LN) cells [110].

Glycyrrhiza uralensis Fisch.

In earlier research, licorice polysaccharides from *G. uralensis* (GP) showed immunomodulatory activity *in vitro* [111]. In another study, licorice component 18-glycyrrhetinic acid shown immunomodulatory activity by enhanced T cell proliferation and increased blood leukocyte count and spleen weight in mice [112-114]. These studies evaluated licorice polysaccharides for their immunomodulatory activity in CT-26 tumor-carrying BALB/c mice [115]. The crude extract of licorice polysaccharides was dried and the supernatant was enriched and divided into three fractions (GP-A, GP-B, and GP-C) for alcohol precipitation by adding 95% ethanol with stirring. The final alcohol concentration was different for the three fractions. The immunomodulatory activity was determined based on immune organs weight and index. The group treated with GP-B demonstrated a significant increase in the thymus and spleen weight; besides, the immune organ indices displayed a considerable change in spleen and thymus indices. Furthermore, GP-B led to significant lymphocytes; while GP-C showed an increase in the population of CD8+ lymphocytes increases in the population of CD4+, as evaluated by flow cytometry. GP-B affected the production of different serum cytokines; the IL-6 and IL-7 levels increased, while TNFα decreased. These levels measure by a cytokine bead panel assay, which asserted the anti-tumor potential of licorice polysaccharides through modulation in the immune system [115].

Arctium lappa L.

Fructooligosaccharides are the burdock root's main bioactive components. Fructooligosaccharide also regulates intestinal ORA [116-119], lowers blood sugar, regulates fat metabolism [120-124], promotes the absorption of minerals, increases the number of Peyer's patch, and stimulates the production of short chain fatty acids (SCFAs). Burdock fructooligosaccharide-1 was isolated from fresh burdock roots, purified, and evaluated *in vitro* and *in vivo* for its immunomodulatory activity in Kunming mice [125]. In the *in vitro* study, burdock fructooligosaccharide-1, when given at a dose of 1000 µg/mL, stimulated splenic cell proliferation and increased the activity of acid phosphatase in peritoneal macrophages in immune-suppressed mice (as evaluated by MTT assay). In normal mice, burdock fructooligosaccharide-1 at a dose of 200 and 500 mg/kg /day promoted phagocytic and phosphatase activity and NO production in peritoneal macrophages. Furthermore, *in vivo* studies revealed that it increased the immune function and suppressed tumor growth in pretreated S180 tumor-carrying mice [125].

Lepidium meyenii Walp.

Polysaccharides obtained from natural sources [126]

are known to have biological activities, for example, immunomodulatory activity. But only the antioxidant activity of Maca polysaccharides (MC-1) was reported. More activities need further exploration. MC-1, a novel polysaccharide isolated from the plant roots, possesses immunomodulatory activity. In immunostimulating assays, MCI-1 enhanced the pinocytic and phagocytic capacities of RAW264.7 cells at concentrations below 250 μg/mL. Furthermore, it promoted the secretion and expression of NO, TNF-α, and IL-6 by stimulating RAW264.7 cells at a relatively lower concentration of 62.5 μg/mL. It confirmed that CR3, MR, and TLR2 were the primary membrane receptors of MCI-1 polysaccharide on RAW264.7 cells at a dose of 10–80 μg/mL, which led to the activation of MAPK pathways, including p-ERK, p-JNK, and p-p38. Besides, MAPKs activate the NF-κB signaling pathway [127].

Eurycoma longifolia Jack

Few studies have been performed about the polysaccharides of *E. longifolia* and their actions. In an immunostimulation assay, Ali-1, a polysaccharide extracted from the roots of *E. longifolia*, significantly increased the pinocytic and phagocytic activities of RAW264.7 cells. Further, in the neutral red uptake assay, Ali-1 polysaccharide measures the pinocytic activity of cells. The phagocytic potential of RAW264.7 cells towards E. coli was evaluated and determined by a Vybrant phagocytosis assay kit using an ELISA. In both pinocytic and phagocytic activities at 125–2000 μg/mL, Ali-1 Polysaccharides increased cytokine (NO, TNF-α, and IL-6) secretion in a dose-dependent manner [128].

Ligustrum vicaryi Rehder

L. vicaryi presents chlorophyll-less phenotype and uses as a horticultural shrub owing to its golden leaves [129,130]. According to the gas-exchange characteristics and chlorophyll fluorescence responses, *L. vicaryi*. can resist SO_2 and thus, can be used for the phytostabilization of Cd-contaminated soil [131-133]. Although *L. vicaryi*. has high ornamental and environmental protection value, its therapeutic potential is yet to elucidate. A polysaccharide isolated from the fruit of *L. vicaryi* exhibited modulation in the immune system by activating the innate and adaptive systems, as studied in a cyclophosphamide-prompted immunocompromised mouse model. When administered to animals at doses of 100, 200, and 400 mg/kg per day, the polysaccharide drastically improved the index of immune organs to stimulate immunity in a dose-dependent manner.

Moreover, the doses of 200 mg/kg and 400 mg/kg enhanced the phagocytic activity of neutrophils in Kunming mice. Furthermore, it improved IL-10 and TNF-α expression dose-dependent, as inferred from ELISA. The oxidative stress and liver damage caused by cyclophosphamide were also lowered [134].

Plant extracts with immunomodulatory activity

Apart from the plants listed in this paper, various additional plant extracts demonstrated immunomodulatory activities, suggesting that they might be helpful to immune modulation. Table 2 lists the essential plants and their traditional usage.

Stachytarpheta cayennensis (Rich.) Vahl

The leaves of *S. cayennensis* previously reported to possess potent analgesic, antimalarial, and anti-inflammatory effects [135-137]. The present study investigated the immunomodulatory potentials of methanol extract of *S. cayennensis* (MESC) leaves on cellular and humoral immune responses and assessed its synergistic effect with artesunate, a standard antimalarial agent with immunomodulatory potentials. The methanolic extract of its leaves was evaluated for immunomodulatory activity *in vivo*. Artesunate, a derivative of artemisinin isolated from Artemisia annua, combined with MESC flooded in a sterile glass slide smeared with rat's blood, possessed significant phagocytic activity at 100 μg/mL with the highest percentage of phagocytic stimulation. Moreover, at 500 mg/kg, the extract inhibited DTH response in adult Swiss albino mice. Whereas a dose of 250 mg/kg of the extract significantly stimulated the humoral immunity, a dose of 250 mg/kg displayed the highest percentage of leucocyte mobilization in Swiss albino mice [138].

Aegle marmelos (L.) Corrêa

The fruit of *A. marmelos* contains many functional and bioactive compounds such as carotenoids, phenolics, alkaloids, coumarins, flavonoids, terpenoids, and other antioxidants. In addition, it also has many vitamins and minerals, including vitamin C, vitamin A, thiamine, riboflavin, niacin, calcium, and phosphorus [139]. Therefore, the chemical profile indicates *A. marmelos* as a good source of immunomodulatory agents. Further, the plant's fruit has been used for many disorders such as chronic diarrhea and dysentery and acts as a tonic for the heart and brain. It is used in indigenous traditional medicine for various disorders, including immunodeficiencies. When used at a dose of 100 and 500 mg/kg, the methanolic extract of *A. marmelos* fruit showed a significant increase in neutrophil adhesion in Wistar albino rats. Besides, the carbon clearance test revealed an increased phagocytic index in Swiss albino mice. Additionally, albino mice treated with the methanolic extract of *A. marmelos* fruit and Ocimum sanctum increased the hemagglutinating antibody titers. Thus, *A. marmelos* stimulated cell-mediated and humoral immune responses at low and high doses [140].

Gentiana olivieri Griseb

Traditionally, the plant *G. olivieri* is used to treat various disorders. The plant report to be sudorific in Ayurveda [141], widely used in east and south-east Anatolia as a bitter tonic, stomachic and to combat some mental disorders in the different regions of Turkey. The macerated dried flowering herb in water is used to lower the blood pressure in type-2 diabetic patients; while infusion (2%–3%) is used as appetizer and antipyretic. The plant is known to possess several alkaloids, triterpenoid acids, fats, bitter secoiridoids glycosides, flavonoids (iso-orientin and its derivatives) and xanthones [142-144]. The ethanol extract and butanol fraction from the aerial parts of *G. olivieri* were evaluated for their immunomodulatory activity on cellular and humoral responses in BALB/c mice by different immunomodulatory assays. At doses of 50, 100, and 200 mg/kg, the ethanol extract and butanol fraction of *G. olivieri* augmented both primary and secondary antibody titers.

Additionally, the ethanol extract at 200 mg/kg and butanol fraction at 100 and 200 mg/kg demonstrated potential effects in the delayed-type hypersensitivity test. Butanol fraction at 100 mg/kg showed a significant rise in the phagocytic index in the *in vivo* carbon clearance test. Therefore, the butanol fraction was inferred to possess potent immunomodulatory effects on cell-mediated and humoral immune responses [145].

Rhaphidophora korthalsii Schott

Various extracts of *R. korthalsii* used traditionally for cancer treatment are shown by researchers to exert a cytotoxic effect on different cancerous cell lines [146,147]. This effect is mainly by the presence of 5,6-dihydroxyindole (DHI), which showed cytotoxic activity against p388 and nonmelanocytic cancerous cell lines [148]. Studies have also demonstrated that an *R. korthalsii* methanol extract stimulated the proliferation of mice splenocytes and human PBMC [149]. As a result, they concluded that this plant extract might help boost the immune system to fight various diseases, including cancer. T cell and NK cell phenotyping, immune cell proliferation, and *in vivo* splenocyte cytotoxicity in BALB/c mice are used to estimate the immunomodulatory activity of an ethanol extract of *R. korthalsii* leaves. The mice injected with 350 and 700 μg/mouse of the extract demonstrated increased splenocyte and bone marrow proliferation. Furthermore, in NK cell immunophenotyping, the extract improved the NK cell population when used at a concentration of 350 μg/mouse. As seen on ELISA, the extract increased the plasma IFN-γ and IL-2 levels at 700 and 350 μg/mouse concentrations [150].

Amorphophallus commutatus (Schott) Engl.

Traditional healers have used corns of this plant for treating various ailments. *A. commutatus* is a red listed edible medicinal plant with a global vulnerable status. The tubers of *A. commutatus* are used for preparing traditional cuisines, treating various ailments such as mouth diseases [151], and making an antidote for snake bites [152] and scabies by conventional medical practitioners. Our lab pioneered reporting this edible tuber's antibacterial and hepatoprotective activities [153]. Toxicity studies revealed that the tuber extract is safe for long-term oral administration, fulfilling the fundamental priority for traditional medicinal uses. In the *in vitro* splenocyte proliferation assay, the methanolic extract of *A. commutatus* exhibited a significant mitogenic effect on splenocytes and an aco-mitogenic effect on phytohemagglutinin (PHA), Concanavalin A (Con-A), and LPS-stimulated splenocytes derived from mouse spleen in a dose-dependent manner. LPS-activated splenocytes showed the highest splenocyte proliferation, followed by Con-A and PHA. In the *in vivo* study, the methanolic extract of *A. commutatus* (at 400 mg/kg body weight) significantly increased the circulating hemagglutinating antibody titer. Furthermore, it caused an increase in the antibody-producing cells in the plaque-forming assay and increased qualitative hemolysis and delayed-type hypersensitivity reaction in a dose-dependent manner [154].

Momordica charantia L.

M. charantia has immunostimulant and immunosuppressive properties [155]. Plant fruits have shown to stimulate phagocytic activity, and splenocyte activation [156-160]. In this study, diethyl ether and methanol extracts of *M. charantia* leaves demonstrated *in vitro* and *in vivo* immunomodulatory activity in phagocytic cells and outbred albino mice infected with *Salmonella typhi* (obtained from ailing patients). As in all diseases, containment of Salmonella infection depends on an intact T-lymphocyte system, including macrophage function. Patients with impaired T-cell function because of lymph proliferative disorders or immunosuppressive medication and patients with disorders that cause “macrophage blockade” such as hemoglobinopathies, malaria, and schistosomiasis are well known to be at risk of serious consequences of Salmonella infection. In the *in vitro* assay, the extracts significantly increased the adherence of carbon particles and the production of NO, superoxide anion, and lysosomal acid phosphatase by neutrophils and macrophages at a concentration of 40–640 μg/mL. This result confirmed that the extract was capable of immunostimulation of phagocytosis. In the *in vivo* leucocyte mobilization, the methanol and diethyl ether extracts elevated the total leucocyte count at 500 and 1000 mg/kg concentrations and improved the antibody titer against the antigen [161].

Moringa oleifera Lam.

M. oleifera is a common herb that contains a variety of compounds, macronutrients, and micronutrients that contribute

to its extensive medicinal value, which includes the treatment of diseases such as asthma, bronchitis, mastitis, skin conditions, worm infestations, and HIV/AIDS symptoms, among others. Its capacity can cure most illnesses based on nutritional and immunomodulatory qualities, including antioxidant and anticancer activities [162]. The plant is readily accessible and utilized as an immunity booster by local people and traditional herbalists in Uganda to treat various illness problems [163]. Previous research on the use of *M. oleifera* and activated charcoal on intoxicated Wistar albino rats with lead acetate revealed improvements in biochemical and hematological parameters and protective benefits on numerous organs and tissues such as the liver and kidneys [164]. Moreover, *M. oleifera* leaf extracts have shown to exhibit immunomodulatory action in immunocompromised cyclophosphamide Wistar albino rats [165,166]

In the neutrophil adhesion test, the highest mean percentage of neutrophil adhesion was seen in the group of animals that received 1000 mg/kg body weight and in those who received 500mg/kg body weight [167]. Moreover, there was a statistically significant elevation in the percentage footpad thickness increment in the group that received 1000 mg/kg body weight of the extract up to 24 hours. Also, there was a dose-dependent increase in the mean hemagglutination antibody titer to SRBC from 10.73 ± 0.57 HA units/µL for the 250 mg/kg body weight to 26.22 ± 1.70 HA units/µL for the 1000 mg/kg body weight. Thus, the plant exhibited immunostimulatory activity on cell-mediated and humoral immune responses in the Wistar albino rats [167].

Trichopodium zeylanicum (Gaertn.) Thwaites

T. zeylanicum (Synonym: Trichopus zeylanicus Gaertn.) is a health tonic and rejuvenator [168]. Immunomodulatory activities have been discovered in *T. zeylanicum* [169]. Swiss albino mice treated with the alkaloid fraction of *T. zeylanicum* obtained from the methanol extract at doses of 75,150, and 300 mg/kg showed a significant increase in the percentage of neutrophils, DTH reaction, and peripheral blood count (WBCs, RBCs, and hemoglobin) in various *in vivo* models [170].

Schwartzia brasiliensis (Choisy) Bedell ex Gir.-Cañas

Dengue virus (DENV) has been shown to infect a variety of cells *in vivo* [171,172] and *in vitro* [173-180], including dendritic cells, monocytes, hepatocytes, and endothelial cells. After infection, infected cells become activated, generating pro-inflammatory mediators such as TNF, IL-6, and IL-8, among others, which damage the integrity of the endothelial cell layer, presumably causing vascular leakage [181-184]. On the other hand, monocytes may be implicated in protective mechanisms by releasing IFN-γ in response to DENV and activating as CD14high CD16+ monocytes that express Toll-like receptors and limit exaggeratedly inflammatory responses, perhaps through IL-10 production [185]. It has demonstrated that *Uncaria tomentosa* extracts had immunomodulatory effects in a DENV-2 infection model of primary human monocytes, decreasing TNF-α production and exhibiting antiviral activity [186]. In the DENV-2 infected monocyte model, the ethanol crude extract of the leaves of *S. brasiliensis* (Synonym: *Norantea brasiliensis* Choisy) and its three partitioned fractions, such as dichloromethane, ethyl acetate, and butanolic fractions, possessed immunomodulatory and antiviral activities *in vitro* [187]. The monocytes treated with ethanol crude extract or ethyl acetate fraction showed no notable changes. But, when the affected monocytes treat with dichloromethane fraction and butanolic fraction, they exhibited notable changes in cytokine inhibition, especially TNF-α. The ethanol crude extract, dichloromethane fraction, and butanolic fractions also reduced the production of IFN-α in dengue-infected cells. However, the ethyl acetate fraction did not exert immunomodulatory activity [187].

Phyllanthus muellerianus (Kuntze) Exell

Various components of the *P. muellerianus* are traditionally used in West Africa to treat digestive problems such as dysentery, constipation, and diarrhea [187-189]. Because of its widespread use in folk medicine, *P. muellerianus* have studied for its effects on immunological responses. In the DTH reaction (cellular responses), the ethyl acetate fraction (at low and high doses) evoked both inhibition and elevation of footpad swelling (pedal edema) in Sprague-Dawley mice. Similarly, the methanol extract at 50 mg/kg caused a remarkable increase in the antibody titer in Sprague-Dawley mice in a non-dose-dependent effect. Notably, the ethyl acetate fraction showed a 100% increase in antibody titers (humoral response) compared with the other fractions [190].

Alstonia scholaris (L.) R. Br.

Based on prior research, the immunomodulatory activity of alkaloids and triterpenes isolated from *A. scholaris* leaves was tested in tumor-bearing C57BL/6 mice and A549 cells [191]. The methanolic and chloroform extracts of *A. scholaris* produced an increase in the DTH reactivity (footpad reaction) of Wistar albino rats with cellular responses in a dose-dependent manner. Furthermore, the methanolic and chloroform extracts at 400 mg/kg showed the highest phagocytic index. Moreover, the groups treated with these extracts at 200 and 400 mg/kg doses demonstrated increased RBC, WBC, and HB counts [192].

Conclusion

Plant-derived natural compounds can be used for developing novel therapeutic agents. Over the years, several plant-extracted compounds have been recognized for their immunomodulatory activity in both humoral and cell mediated immunity with use in various immune system-related diseases, thereby serving as an effective alternative to immunomodulators. To counteract the drawbacks of immunomodulatory drugs, it is important to isolate plant compounds with immunomodulatory activity. Further investigation can be conducted to isolate the compound from plant extract which possesses immuno-

modulatory activity. Since more plant-derived natural products with fewer side effects and low cost must be produced, attention must be paid to the market and logistic factors. Improvement of the clinical study design to ensure the therapeutic safety of herbal drugs is also warranted.

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Conflict of Interests
The authors have no conflict of interest to declare.

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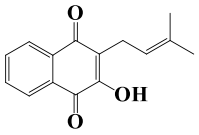
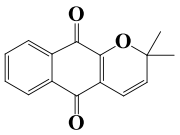
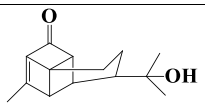
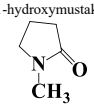
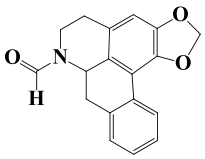
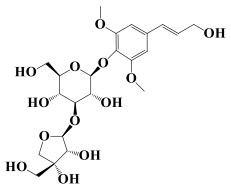
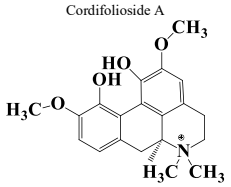
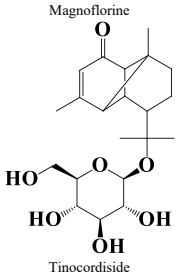
Table 1. Traditional uses of plants and structures of isolated compounds

S.no	Plants Name	Family	Traditional Use	Structures
1.	*Stereospermum chelonoides* (L.f.) DC.	Bignoniaceae	Various parts of the plant are used in folk medicine for the treatment of diabetes, diuretic, pain, fever, inflammations and asthma Various parts of the plant are used in folk medicine for the treatment of diabetes, diuretic, pain, fever, inflammations and asthma Various parts of the plant that used in folk medicine for the treatment of diabetes, diuretic, pain, fever, inflammations, and asthma [193].	 Lapachol  Dehydro-α-lapachone  11-hydroxymustakone  N-methyl-2-pyrrolidone  N-formylannonain
2.	*Tinospora sinensis* (Lour.) Merr.	Menisper maceae	Traditional ayurvedic medicine has used the plant for ages to treat fever, jaundice, chronic diarrhea, cancer, dysentery, bone fracture, pain, asthma, skin disease, poisonous insect, snake bite, and eye disorders [194].	 Cordifolioside A  Magnoflorine  Tinocordiside

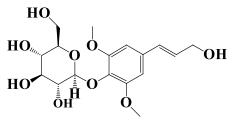
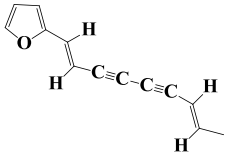
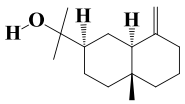
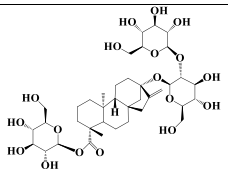
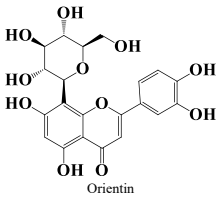
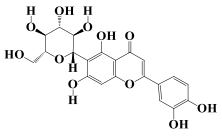
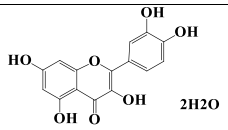
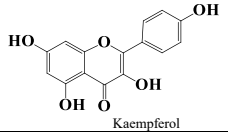
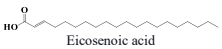
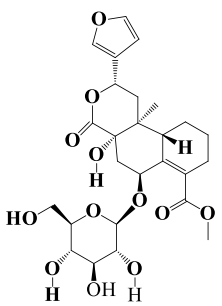
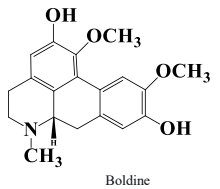
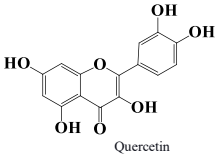
				 Syringin
3.	*Atractylodes lancea* (Thunb.) DC.	Asteraceae	Treating cold and dampness, curing headache, eliminating phlegm and water-retention, removing the swelling of wind and water between the skin, stopping heart disease and vomiting in cholera, warming the stomach and eliminating food [195,196].	 Atractylodin  β-eudesmol
4.	*Stevia rebaudiana* (Bertoni) Bertoni	Asteraceae	For centuries, Brazilian and Paraguayan natives used the plant's leaves as a sweetener and commonly used as food additives [197].	 Stevioside
5.	*Phyllostachys bambusoides* Siebold & Zucc.	Poaceae	Phyllostachys bambusoides is used in Ayurvedic medicines as a cooling tonic, to treat cough and asthma, and even as an aphrodisiac [198].	 Orientin  Iso-orientin
6.	*Cassia fistula* L.	Leguminosae	Treating chest diseases, stomach troubles, to treat skin infections, and fever [84].	 Quercetin dehydrate  Kaempferol
7.	*Tinospora crispa* (L.) Hook. f. & Thomson	Menisper maceae	Traditionally in treating jaundice, rheumatism, urinary disorders, fever, malaria, diabetes, internal inflammation, fracture, scabies, hypertension, reducing thirst, increasing appetite, cooling down the body temperature, and maintaining good health [199].	 Eicosenoic acid  Cordioside  Boldine  Quercetin

Table 2. Traditional uses of plants

S.no	Plants name	Family	Traditional use	References
1.	*Dendrobium catenatum* Lindl.	Orchidaceae	They are traditionally used as medicinal herbs in treating various disorders, such as nourishing the stomach, enhancing the production of body fluids, or nourishing Yin.	[200]
2.	*Chlorophytum borivilianum* Santapau & R.R.Fern.	Asparagaceae	They are traditionally used for rejuvenating, aphrodisiac, and natural sex tonic properties and effectively alleviate sexual disorders.	[201]
3.	*Eupatorium adenophorum*	Asteraceae	They are traditionally used as conventional medicine in treating fever, desinsectization, traumatism, and phyma in China.	[202]
4.	*Clerodendrum splendens* G.Don	Lamiaceae	Indegenous people traditionally use them to treat shingles, spleen in children, asthma, rheumatism, ulcers, and malaria.	[203]
5.	*Glycyrrhiza uralensis* Fisch.	Fabaceae	They are traditionally used to treat many diseases, such as respiratory disorders, hyperdipsia, epilepsy, fever, sexual debility, paralysis, stomach ulcers, rheumatism, skin diseases, hemorrhagic diseases, and jaundice.	[204]
6.	*Arctium lappa* L.	Asteraceae	They are traditionally used to treat diseases such as sore throat and infections such as rashes, boils, and various skin problems.	[205]
7.	*Lepidium meyenii* Walp.	Brassicaceae	Treating sexual dysfunction, osteoporosis, benign prostatic hyperplasia, memory and learning, depression, and anxiety.	[206]
8.	*Eurycoma longifolia* Jack	Simaroubaceae	Most popular folk medicines for their aphrodisiac effects and treatment of intermittent fever (malaria).	[128]
9.	*Ligustrum vicaryi* L	Oleaceae	Traditional Chinese Medicine (TCM) the plant is used for liver cancer treatment, and that confirmed to effectively control cancer progression. improve the quality of life, and prolong survival times to some extent in liver cancer patients.	[207]
10.	*Stachyatarpheta ceyennensis*	Verbenaceae	Traditionally used medicine for antipyretic, antidiarrheal, liver treatment, suppressing cough, lowering blood sugar.	[208]
11.	*Aegle marmelos* (L.) Corrêa	Rutaceae	Herbal medicine for the management of diabetes.	[209]
12.	*Gentiana olivieri* Griseb	Gentianaceae	Traditional medicine uses them as an antidiabetic, hepatoprotective, digestive aid, antidepressant, and antianemic.	[210]
13.	*Rhaphidophora korthalsii* Schott	Araceae	The plant uses in Chinese traditional medicine for cancer.	[150]
14.	*Amorphophallus commutatus* (Schott) Engl.	Araceae	Tuber paste of the plant is applied externally to cure scabies.	[211]
15.	*Momordica charantia* L.	Cucurbitaceae	Used in Asian traditional medicines for the treatment of cholera, anemia, ulcer, diarrhea blood diseases, bronchitis, gout, dysentery, worms, gonorrhea, rheumatism, colic, illness of the liver and spleen, cancer, diabetes, etc.	[212]
16.	*Moringa oleifera* Lam.	Moringaceae	Traditional uses of the genus are healing skin infections, anxiety, asthma, wounds, fever, diarrhea, and sore throats.	[213]

17.	*Trichopodium zeylanicum* (Gaertn.) Thwaites	Dioscoreaceae	The indigenous tribal community in Agastya hills traditionally uses this plant as an instant energy booster.	[214]
18.	*Schwartzia brasiliensis* (Choisy) Bedell ex Gir.-Cañas	Marcgraviaceae	Treating dengue	[187]
19.	*Phyllanthus muellerianus* (Kuntze) Exell	Phyllanthaceae	The whole plant used in gonorrhea, menorrhagia, and other genital infections	[215]
20.	*Alstonia scholaris* (L.) R. Br.	Apocynaceae	They treat malaria, abdominal disorders, dyspepsia, leprosy, skin diseases, tumors, chronic and foul ulcers, asthma, bronchitis, helminthiasis, agalactia, and debility.	[216]

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