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Original Article

Plant Bioactive Compounds In Immunomodulation: From Molecular Mechanisms To Clinical Prospects Review

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ABSTRACT

The immune system is a coordinated network crucial for defending against infections and maintaining health. Dysregulated immune responses can lead to various disorders, necessitating effective immunomodulatory therapies such as immunostimulants, immunosuppressants, and immunoadjuvants. However, long-term synthetic drug use frequently has negative side effects, highlighting the need for safer alternatives. Recently, plant-derived bioactive substances have gained attention for their pharmacological properties and ability to modulate immune responses through diverse pathways, emphasizing the therapeutic potential of medicinal plants as natural immunomodulatory agents. Bioactive phytochemicals with immunostimulatory, immunosuppressive, anti-inflammatory, antioxidant, and adjuvant properties—such as polysaccharides, flavonoids, polyphenols, terpenoids, and alkaloids—are given particular attention. *Bletilla striata, Dryopteris cochleata, Baccharis dracunculifolia, Codonopsis pilosula, Bidens pilosa L, Ziziphus jujuba, Flourensia cernua, Siraitia grosvenorii, and Ficus hirta* are among the medicinal plants that have been shown in recent research to have the ability to control immune responses via pathways like NF-κB, MAPK, and TLR-mediated signalling. All things considered, the evidence that is now available indicates that bioactive compounds produced from plants are attractive candidates for the creation of new immunotherapeutic agents, functional meals, and vaccine adjuvants.

Keywords: immune system, immunodeficiency problems, autoimmune disorders, infectious diseases, Bioactive phytochemicals.

INTRODUCTION

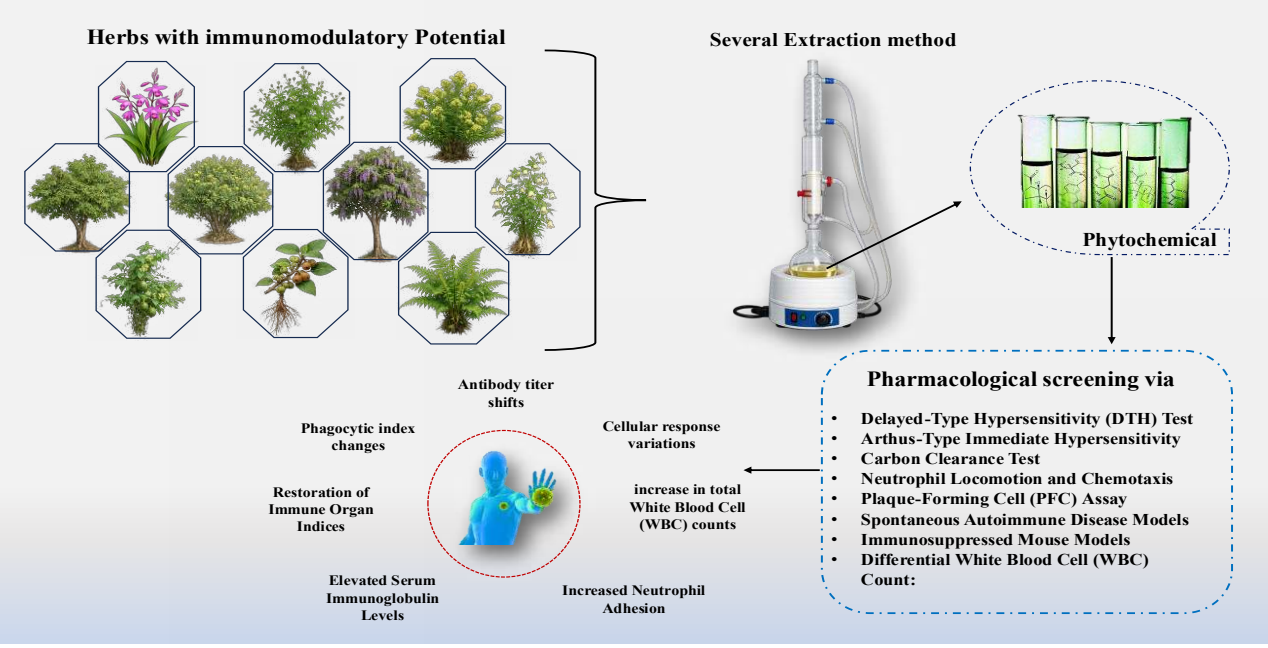

Figure 1: Experimental Framework for Assessing the Immunomodulatory Activity of Medicinal Plants

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The immune system is a sophisticated network of cells and biological mediators that protects the body from damage caused by outside invaders like pathogens and the infiltration of cancerous cells while limiting over-activation of the immune system. [1]. It is characterized by both innate and adaptive immunity, which cooperate to keep the body safe**.** Numerous internal and environmental factors can affect the immune system's effectiveness, potentially leading to malfunction [2]. An abnormally triggered immune response is brought on by autoimmune conditions such celiac disease, type I diabetes, Addison's syndrome, Graves' disease, and rheumatoid polyarthritis, as well as infectious diseases as COVID-19 and dengue fever [3]. For instance, the illness is worsened by the dengue virus's interaction with immune cells, which results in a cytokine storm that includes tumour necrosis factor α, IL1β, and IL6. Self-reactive T cells and an excess of antibodies directed against the body's tissues also cause persistent inflammation in autoimmune diseases. For both kinds of disorders, immune response regulation is crucial [4].

Any alteration of the immune response is referred to as immunomodulation, and it might consist of a part or stage of the immune response being induced, triggered, amplified, or suppressed. The idea of immunomodulation has drawn a lot of attention, especially in light of the recent rise in infectious diseases [5]. Immunostimulants, immunoadjuvants, and immunosuppressants are three types of immunomodulators. Immune cells are vital to human health, especially when it comes to coordinating an immune response by secreting cytokines and interacting with other cells [6]. Cytokines are divided into many groups, such as chemokines, interleukins, and interferons, based on the characteristics of their receptors. Cytokines released by immune cells can alter the production of other cytokines as well as initiate or prevent inflammatory responses [7]. Depending on how they work, cytokines can be classified as either pro-inflammatory or anti-inflammatory. Proinflammatory cytokines, including interleukin-1 (IL-1), IL-6, and tumor necrosis factor-alpha (TNF-α), are primarily responsible for the start and amplification of immune responses [8]. These cytokines are created in reaction to tissue injury, infection, or other inflammatory stimuli. Pro-inflammatory cytokines increase blood vessel permeability, encourage the creation of acute-phase proteins, and aid in the recruitment and activation of immune cells to inflammatory areas [9]. Transforming growth factor-beta (TGF-β) and IL-10 are examples of anti-inflammatory cytokines that reduce and resolve immune responses. These cytokines aid in preventing excessive inflammation by opposing the effects of pro-inflammatory cytokines. Anti-inflammatory cytokines support tissue regeneration and repair, control immune cell activity, and preserve immunological homeostasis [10].

Pharmacological substances known as immunostimulants bolster the body's defences against infection. By boosting the immune response, they serve as prophylactics and potentiators in healthy people [11]. They can be used in immunotherapy for those with weakened immune systems. Particularly promising for the treatment of cancer are immunostimulants. To treat autoimmune illnesses, immune-related disorders linked to infections, and organ transplant rejection, immunosuppressants are crucial. By raising vaccine antigenicity without having a particular antigenic effect, immunoadjuvants boost the immune system [12]. They serve as depots for the antigen's gradual release, assist immune cells in targeting antigens, and regulate and strengthen the type of immune response that is elicited. Th1 and Th2 responses, which include cellular and humoral options, as well as immunological defense, immune destruction, and regeneration, can all be impacted. These are an innovative and fascinating application of immuno-adjuvants [13].

Despite the many advantages of synthetic immunomodulatory medications, their unfavorable side-effect profile and extensive effects on the immune system are significant obstacles to their long-term use, which justifies the quest for safer and more effective agents with tailored immunomodulatory action. Utilizing natural materials as immunoadjuvants to boost immunogenicity during vaccine development is quite optimistic [14]. According to previous investigations, natural compounds with immunomodulatory properties have already been utilized to treat inflammatory conditions, cancer, and autoimmune diseases. The physiologically active secondary metabolites included in these materials include alkaloids,

polysaccharides, terpenoids, flavonoids, coumarins, glycosides, and proteins [15].

Recent decades have seen research into the immunomodulatory qualities of plant extracts, which have been developed as complementary or alternative treatments. Herbal medicines are sometimes used as alternative remedies because they may be more effective and have fewer side effects than contemporary medicine [16]. Actually, a number of studies have shown that herbal treatments are adequately successful in treating a variety of ailments, including various cancers and infectious diseases.

Interestingly, herbal treatments account for between 30 and 50 per cent of all prescription medications in China, while 80 per cent of Africans use them as their primary treatment for several illnesses [17]. In India, herbal medicine has been and still is used to treat and prevent a number of ailments. However, the Thai Herbal Pharmacopoeia's list of Thai plants' immunomodulatory qualities is not very comprehensive [18]. The pharmacological effects of herbal bioactive compounds that either activate or inhibit cytokines have been reported in numerous studies [19]. For example, it has been shown that Scutellaria baicalensis Georgi's baicalein and baicalin inhibit HIV infection and replication by triggering interferon. Furthermore, Radix Stephaniae Tetrandrine, which is obtained from the dried root of Stephania tetrandra S. Moore, has demonstrated anticancer effects by altering a number of pathways, including the initiation of apoptotic pathways, the reduction of inflammatory processes, and the suppression of cellular proliferation [20].

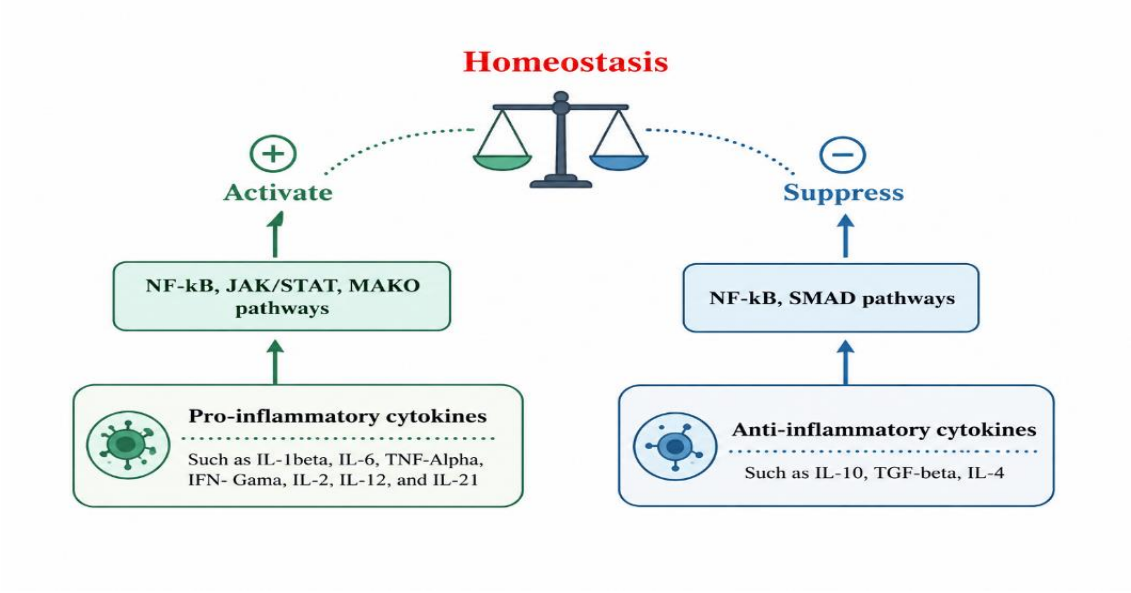

Figure 2: Schematic showing how pro- and anti-inflammatory signalling pathways control immunological homeostasis.

1.1. Immune System

Through the physical barrier and robotic, electric, or molecular reaction communication of particular cells and organs, it serves as a defense system for people against endogenous and external chemical and biotic invaders [21]. Antigens, or microbes—infection-causing organisms including bacteria, viruses, parasites, and fungus, or any agent that causes harm and illness—are the biotic "foreign" invaders. As soon as an antigen comes into contact with a cell, the immune system recognizes it and separates it from non-self-substances [22]. The immune system cell detects the self-substance as a component of the host organism due to cell recognition. Non-self-molecules, on the other hand, are alien substances that are not a part of the host organism [23]. Non-self-substances, such as antigens, can elicit an immune response by stimulating the formation of antibodies against them and then selectively mixing with them. Antibodies are produced by the release of cytokines by the antigen-presenting cell. The immune system's response to healthy cells and tissues is what causes autoimmune diseases [24].

1.2. Type of immunity:

The two primary forms of human defense against infection are innate immunity and adaptive immunity. It has long been believed that innate immunity serves as the first line of defences against pathogens [28]. Physical barriers like hair, mucus, and skin; chemicals like tears in the eyes and salt in the skin; blood proteins; phagocyte cells like macrophages and dendritic cells (DCS); mast cells; neutrophils; basophils; eosinophils; and invariant natural killer cells like NK cells, NKT cells, and gd T cells are all examples of innate immunity [29]. When normal cells and innate immune cells fight infections, they release cytokines. These chemicals cause adaptive immunity. Antibodies are then produced by adaptive immunity. Adaptive immunity is influenced by T and B cells as well as humoral elements such as immunoglobulin and macromolecule-like antibodies in blood plasma cells [30]. It uses various kinds of antigen receptors that are produced de novo by DNA rearrangement processes in the somatic immune organs of mammals rather than being encoded in germline cells [31].

1.2.1. Innate immunity

The first line of protection against infections is innate immunity. Although this type of immune response is quick, it is not selective and lacks immunological memory. Epithelial barriers and phagocytes—a group of myeloid cells that includes dendritic cells, neutrophils, blood monocytes, and tissue macrophages—are involved [32]. The complement system, tissue-resident immune cells, and natural killer (NK) cells are other components of the innate immune response. The paracrine release of leftover MSCs, which can alter tissue macrophage activities, is one way this kind of immunity is regulated [33]. Tocilizumab for COVID-19, ustekinumab and ixekizumab for plaque psoriasis, and dupilumab for atopic dermatitis are examples of monoclonal antibodies that act as interleukin inhibitors. Sarilumab was used in conjunction with additional monoclonal antibodies to treat melanoma in a phase 2 experiment [34]. By focusing on the NLRP3 inflammatory pathway, certain antidepressants, such as tianeptine and fluoxetine, may have beneficial anti-inflammatory effects. Fingolimod (FTY-720), which is used to treat multiple sclerosis [35], promotes M2 microglia polarization while inhibiting NLRP3 inflammasome assembly and lowering TNF-α, IL-6, and IL-1β levels. Furthermore, progasdermin D proteins are cleaved by caspase-1, which contributes to pyroptosis, a unique type of cell death [36].

Another element of cellular innate immunity is NK cells, which are capable of producing chemicals that kill cells. They don't require specific antigens to activate them in order to respond immediately to a disease [37]. All nucleated cells in the body have major histocompatibility complexes I (MHCI) on their surface, which protects them from damaging NK-cell activity and suppresses it. During certain viral infections or the development of cancer, body cells may block MHCI production [38], which leads NK cells to recognize them as non-self and eliminate them. T lymphocytes' release of IL-22 can indirectly reduce NK cells' capacity to fight cancer cells by changing the expression of CD155 on the surface of cancer cells [39].

While a focused immune response is required for more severe infections caused by certain bacteria, A basic first line of defences against infections is the innate immune system [40]. Antigen-presenting cells (APCs) that transport antigens to the adaptive immune system include B cells, macrophages, and dendritic cells. Digested pathogens are transported by dendritic cells to lymph nodes, where they use MHCII complexes to deliver antigens to naive T helper cells (Th0) [41]. B7 proteins (CD80/CD86) attaching to T cell CD28 give co-stimulation from APCs, which is necessary for full activation of Th0 cells. This mechanism causes Th0 cells to differentiate into either Th1 cells, which improve cell-mediated immunity and cytotoxic T cell function, or Th2 cells, which support humoral immunity [42]. Activation of the innate immune system promotes the induction of adaptive immunity because cellular innate immune system components such as dendritic cells and cytokines can increase lymphocyte proliferation, differentiation, and survival [43].

1.2.2. Adaptive immunity

The majority of lymphocytes involved in adaptive immunity are T and B cells. With highly specific clonal responses to a wide range of antigens, it offers long-lasting protection. Because it produces immunological memory and self-reactivity, the adaptive immune response is self-limiting and rapidly

diminishes as the infection is eradicated. Immunomodulatory Activities in vitro, ex vivo, and in vivo [44].

1.2.2.1. Cell-mediated immunity

Cell-mediated immunity is a specific adaptive immune response that is initiated by Th1 cells and leads to the activation of APCs and a cytotoxic T-cell response. This immune response fights intracellular infections brought on by some viruses, bacteria, fungus, and protozoa [45]. Th1 cells use TCRs to identify pathogen epitopes presented by APCs via MHCII, which then triggers APC activation through interferon-gamma (IFN-γ) and other signals, including CD40-CD40 ligand. Through MHCI and co-stimulatory signals like B7+CD28, activated APCs interact with cytotoxic T cells to promote T cell activation by releasing IL-2 [46]. Numerous clinical trials are currently assessing the effectiveness of CD40 agonistic antibodies in triggering apoptosis in tumour cells and anti-tumour signalling in immune cells. On the other hand, blocking CD40 signalling is advantageous in treating inflammatory conditions and preventing allograft rejection [47]; for example, siRNA-targeted CD40 gene suppression prolongs the acceptance of allografts in mice. Additionally, therapies that target the co-stimulatory pathways, such as abatacept, have demonstrated potential in clinical studies for the remission of rheumatoid arthritis.

1.2.2.2. Humoral immunity

A particular adaptive immune response triggered by Th2 cells that results in the generation of B cells and antibodies is known as humoral immunity. Extracellular infections, such as those caused by bacteria, fungi, protozoa, and parasites, are combatted by this immune response [48]. Additionally, intracellular infections may be supported by this immune response. When certain antigens activate naive Th0 cells, they develop into Th2 cells and interact with B cells through the TCR–MHCII complex [49]. B cells use MHCII to process and deliver antigens in their capacity as antigen-presenting cells (APCs). A secondary signal is produced when Th2's CD40 ligand interacts with B cells' CD40. Additionally, Th2 cells release cytokines that aid in the formation of B cells [50]. Activated B cells can develop into either memory B cells, which are in charge of identifying secondary pathogens, or plasma cells, which generate antibodies. Numerous transcription factors, including Bcl, E2A, PAX5, FOXO1, NF-kB, and Myc [51], are the subject of ongoing research into the intricate maturation and differentiation processes of B cells within germinal canters. Additionally, recent research has emphasized the potential regulation of B-cell activity by transcriptional enzymes, RNA-binding proteins, and microRNAs [52].

There are several methods that antibodies might kill infections, including: 1) directly binding to toxins and neutralizing them; 2) binding to antigens on pathogen surfaces; 3) agglutinating pathogens to reduce their motility; and 4) opsonizing pathogens to improve phagocytosis. The traditional complement pathway is started by binding to antigens. Additionally, they have the ability to activate effector cells such cytotoxic T cells, NK cells, and dendritic cells [**53**].

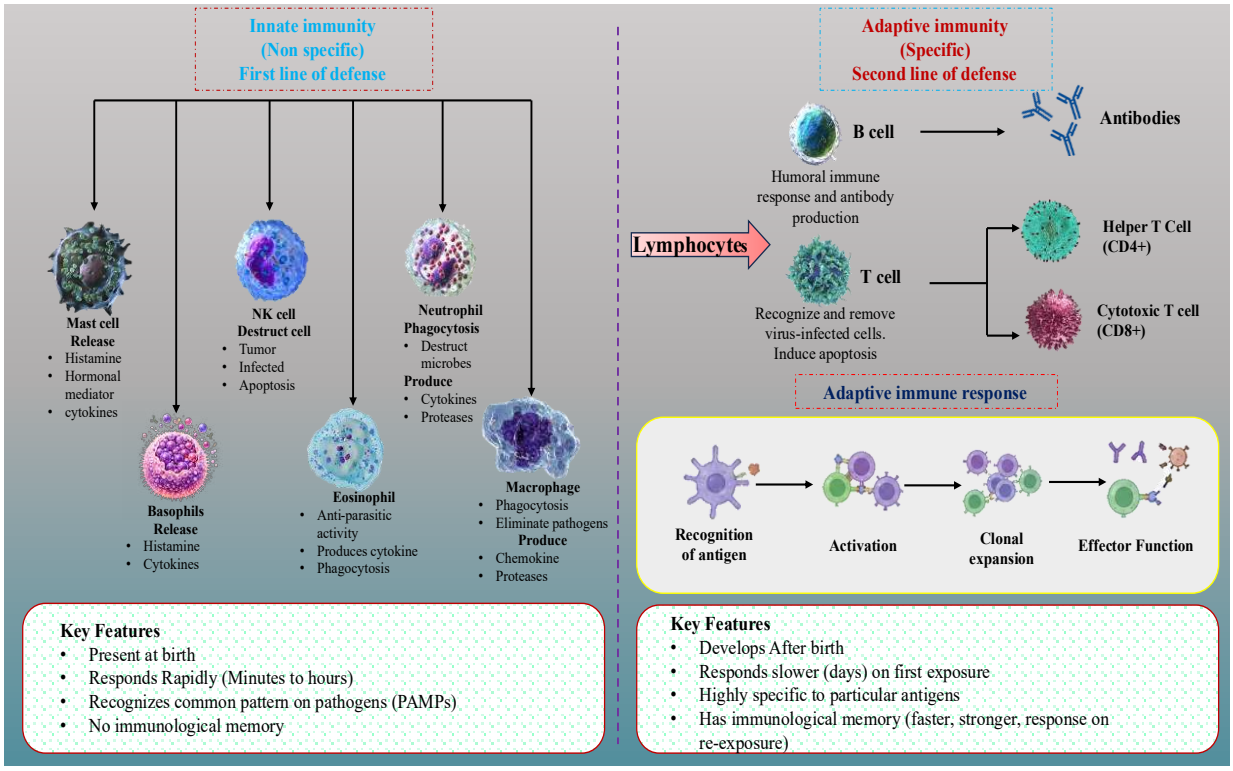

Figure 2: An overview of action and function of immunomodulators

1.3. Subtypes of Immunomodulators

Clinically, immunomodulators can be classified into the following three categories:

1.3.1. Immunoadjuvants

These substances are typically employed in the creation of immunizations to boost immunity. They strengthen the immune system's response to the vaccine's antigenic component. At the cellular or humoral level, adjuvants increase, stimulate, amplify, enhance, activate, or modify the immune response [54]. The most well-known examples are Corynebacterium parvum, Bacillus Calmette-Guérin (BCG), and Freund's adjuvant, all of which include bacterial antigen. Interferon, transfer factor, histamine, IL-1, and tuftsin are examples of endogenous adjuvants. Increased immunological reactivity to many antigens or groups of antigens is the outcome, despite their potentially nonspecific mode of action [55].

1.3.2. Immunostimulants

Additionally, these substances enhance or boost humoral or cellular immune responses. Unlike nonspecific stimulants, some of these are specialized immunostimulants, like vaccinations, which trigger an immunological response to certain antigens [56]. These stimulants are widely used to treat autoimmune disorders, allergies, cancer, and immunodeficiency. In healthy individuals, stimulants act as preventive measures by raising the baseline levels of the immune system. An individual's immune system becomes more active when they are exposed to a pathogen [57], allowing the virus and its byproducts to be swiftly eradicated and averting sickness. In patients with weakened immune systems, stimulants serve as immunotherapeutic drugs. Immunocompromised patients are those who have both primary and secondary immunodeficiencies [58]. A hereditary or developmental immune system failure results in primary immunodeficiency. For example, severe combined immunodeficiency (SCID), X-linked agammaglobulinemia, and Wiskott-Aldrich syndrome (WAS). The loss of immune function caused by exposure to various chemicals, such as AIDS, cancer, cytokines (IL-2, interferons, and G-CSF), microbial poisons or fragments, herbs, venom, and so forth, is known as secondary immunodeficiency [59].

1.3.3. Immunosuppressants

These drugs reduce or inhibit the immune system's ability to function. Intentional and unintentional

immunosuppression are the two main categories. Deliberately induced immunosuppression is necessary to treat autoimmune diseases such rheumatoid arthritis, Grave's disease, and myasthenia gravis, prevent the body from rejecting an organ transplant, and treat graft-versus-host disease following a bone marrow transplant [60]. The first immunosuppressant discovered was cortisone, but its usage was restricted due to adverse effects. However, the discovery of cyclosporine led to an amazing decision, and it is currently utilized in kidney, liver, and heart transplants [61]. Transplantation and graft rejection are also treated with antibiotics such as tacrolimus and sirolimus. Nondeliberate immunosuppression can be brought on by chronic illnesses like HIV, cancer, aging, and malnutrition. In this case, undesired immunosuppression makes people more susceptible to a variety of illnesses, such as those caused by bacteria, fungi, viruses, and protozoa [62].

The following are some clinical uses for immunosuppressants [63]:

• To avoid rejection of donated organs and tissues.

• To address bone marrow transplant recipients' graft-versus-host disease.

• to treat rheumatoid arthritis, psoriasis, ulcerative colitis, myasthenia gravis, and systemic lupus erythematosus, all of which have autoimmune components in their pathophysiology that are not fully understood.

• Preventing Rh haemolytic disease in infants undergoing selective immunosuppression.

1.4. Immunity-Related Disorder

The two types of immunity-related disorders are autoimmune disease and immunodeficiency. Autoimmune illnesses are caused by the immune system's response to its own healthy cells and tissues. Some inflammatory disorders, plaque psoriasis, and rheumatoid arthritis are examples of autoimmune diseases [25]. Primary and secondary immunodeficiency diseases are the two types of immunocompromised illnesses. Primary immunodeficiency disorder (PIDD) is caused by a genetic abnormality in immune cells. Approximately 130 kinds exist [26]. Diseases or environmental factors like HIV, malnutrition, and medical treatments like chemotherapy can result in secondary immunodeficiency disorders. COVID-19, AIDS, cancer, and SARS are the most well-known secondary immunodeficiency illnesses [27].

1.5. Etiology

The "etiology of immunomodulatory activity" is not a disease or condition with a specific cause, but rather the origin and underlying mechanisms of substances or processes that change the immune system's response. This activity could result from a natural biological process (such a host's response to infection) or from a therapeutic intervention using various drugs known as immunomodulators [64]. Immunomodulators can either increase (immunostimulant) or decrease (immunosuppressive) immune responses in order to treat certain disease processes or restore immune system balance. The "etiology" (origin) of these effects originates from a variety of sources and techniques [65].

1.6. Classic pharmacological approach for immunomodulation

Immunosuppressants can impact the last stages of the humoral response, including the control of the antibody titre and the degree of their affinity, as well as the transcription rate of genes encoding proteins necessary for lymphocyte function [66]. They can impact numerous immune response sites, this being only one of them. Numerous therapeutic domains, including the management of autoimmune diseases and transplantation, include non-steroidal anti-inflammatory drugs (NSAIDs), histamine antagonists (HAs), corticosteroids, and various cellular signalling inhibitors [67].

Immunomodulators	Category	Example	Mechanism	Main side effects
Immunosuppressant	Inhibitors of	Glucocorticoids	reduced extravasation of leukocytes. Decrease the	Children's growth retardation, inherited osteopenia, bone necrosis,

	lymphocyte gene expression. Inhibitors of lymphocyte signalling		expression of pro-inflammatory cytokines.	hyperglycaemia, and hypertension.
		Cyclosporine	Antigen-triggered signal transduction constrain in T lymphocytes. Lymphokine and anti-apoptotic protein expression should be decreased.	Renal dysfunction, gum hyperplasia, hyperuricemia, hyper-cholesterolemia, diabetogenic.
		Tacrolimus	inhibits calcineurin, which prevents T-cell activation.	Nephrotoxicity, neurotoxicity hypertension, hyperkalaemia, hyperglycaemia.
		Sirolimus	Suppress T-cell activation and proliferation. suppress IL-2 and the T-cell growth factor receptor.	Serum triglyceride and cholesterol levels rise. prolonged delayed graft function and compromised renal function.
	Cytotoxic agents	Azathioprine, azathioprine sodium	prevent purines from being synthesized from scratch, which prevents lymphocyte growth.	leukopenia, thrombocytopenia, pancreas infection, alopecia, GI toxicity, and liver toxicity.
		Mycophenolatm ofetil	Inhibit *de novo* synthesis of guanine by inhibiting inosine monophosphate dehydrogenase	Leukopenia, diarrhea, vomiting, sepsis associated with cytomegalovirus.
	Alkylating agent	Cyclophospham ide	Stop the creation of proteins and cell division by creating cross links between DNA strands.	Heart toxicity, haemorrhagic cystitis and pancytopenia, graft vs host disease syndrome, and electrolyte imbalances.
	Cytokine inhibitors	Etanercept, infliximab, adalimumab, anakinra,	Inhibit TNFα from binding to TNFα receptors via binding with tumor necrosis factor-alpha.	Reactivation of tuberculosis, psoriasis, invasive fungal infections, hypersensitivity, and anaphylaxis.

		daclizumab, basiliximab		
	Antibodies directed against certain molecules of immune cells	Antithymocyte globulin	decrease the number of lymphocytes in circulation by causing cytotoxicity. It attaches itself to cell surface molecules that control cell processes in order to prevent lymphocytes from functioning.	Leukopenia, thrombocytopenia, kidney failure, fever, chills, low blood pressure, and serum disorders.
		Muromunab	Internalize the T-cell receptor to stop further antigen recognition.	High temperature, chills or rigidity, myalgias, arthralgias, aseptic meningitis, circulatory collapse, cardiac arrest, and cytokine release syndrome.
	Intercellular adhesion molecules inhibitors	Efalizumab	Inhibit the LFA-1-ICAM connection to prevent T-cell adhesion and trafficking.	Invasive fungal illness, viral meningitis, bacterial sepsis, and progressive multifocal leukoencephalopathy.
Immunostimulant-lants	Imidazothiazole derivative	Levamisole	Restore the immunological activity of monocytes, macrophages, and B and T cells.	Nausea, muscle soreness, allergic reactions, and flu-like symptoms.
	Recombinant cytokines	Aldesleukin, interferon alpha, interferon gamma.	prevent cell division and boost immune cell functions such T lymphocyte cytotoxicity and macrophage phagocytosis.	anorexia, cardiomyopathy, myocardial infarction, arrhythmias, and hypotension.
	Hormonal analog	soprinosine	Boost the production of cytokines, such as IL-1, IL-2, and IFN-γ. It causes the growth of lymphocytes.	CNS depressant, brief nausea, and elevated serum and urine uric acid levels.

Table 1: Conventional Drug-Based Approaches for Immunomodulatory Therapy [68].

2. Evidence-Based In vitro, ex vivo, and in vivo Immunomodulatory Effects of Medicinal Plants

Medicinal plants have long been known to reduce inflammation and alter immune system function. The therapeutic usage of plants and their derivatives is summarized [69]. It has long been documented in classical books and, more recently, has been widely disseminated through many internet sites, some of which need to be rigorously reviewed for credibility [70]. The immunomodulatory potential of different plant species has been highlighted in a growing number of studies and review publications over the last few decades. The bioactivity of specific plants has been reported in numerous research; these are listed below [71].

Scientific Name	Family Name	Plant part use	Mode of preparation	Chemical compound	References
Bletilla striata	Orchidaceae	tubers	Absolut Ethanol Extraction	polysaccharides, flavonoids, saponins, phenanthrenes, and bibenzyls	Pang et al., 2026
Dryopteris cochleate	Polypodiaceae	leaves	supercritical fluid extraction	phenols, flavonoids, tannins, and terpenoids	Patil et al., 2026
Baccharis dracunculifolia	Asteraceae	leaves	extracted in 70% ethanol	polyphenols, flavonoids, terpenoids, polysaccharides, and cinnamic acid	Cappellucci et al., 2026
Codonopsis pilosulae	Campanulaceae	roots	water extraction	Polysaccharides, saponins, alkaloids, flavonoids	Dong et al., 2026
Lonchocarpus cultratus	Fabaceae	Seeds	successive extractions with hexane, dichloromethane, and methanol	chalcones, polyphenols, and alkaloids	Banhuk et al., 2026
Bidens pilosa L	Asteraceae	Powdered whole plant	ethyl acetate extract	flavonoids and polyacetylenes	Zhu et al., 2026

Ziziphus jujuba	Rhamnaceae	Seeds	defatted by homogenization, ultrasonication	Polysaccharides,	Li et al., 2026
Flourensia cernua	Asteraceae	Whole Plant	fermented extract	caffeic acid, apigenin, myricetin, and quercetin,	Usme-Duque et al., 2026
Siraitia grosvenorii	Cucurbitaceae	Fruit	Using heated water extraction (HWE), acid-assisted extraction (ACAE), alkaline-assisted extraction (ALAE), enzyme-assisted extraction (EAE), and ultrasonic-assisted extraction (UAE) for hot air-dried fruits.	polysaccharides	Jiang et al., 2026
Ficus hirta	Moraceae	Root	hot water extraction (HWE), ultrasound-assisted extraction (UAE), enzymatic-assisted extraction (EAE), and fermentation-assisted (FAE	Polysaccharides, psoralen, flavonoids, and polyphenols	Ju T et al., 2026

Table No: 2 Immunomodulatory Potential of Medicinal Plants and Their Bioactive Constituents

2.1. Bletilla striata

Family: Orchidaceous

Bletilla striata is a hardy, tuberous perennial plant that is indigenous to East Asia. It is often referred to as the Chinese ground orchid or hyacinth orchid. It is a traditional medicinal plant rich in bioactive polysaccharides with notable anti-inflammatory and immunomodulatory properties [72]. A recent study by Pang et al. 2026 reported the isolation and characterization of a novel low-molecular-weight polysaccharide fraction (BSP-2) from plant and evaluated its immunomodulatory potential. BSP-2 was purified through ion-exchange and gel-filtration chromatography, yielding a highly pure neutral polysaccharide with a molecular weight of approximately 4.46 kDa. Structural analyses revealed that BSP-2 is predominantly composed of mannose and glucose residues with a backbone mainly consisting of →4)-β-D-Manp-(1→ and →4)-β-D-Glcp-(1→ linkages. Biological evaluation using LPS-stimulated RAW 264.7 macrophages demonstrated that BSP-2 significantly suppressed. the generation of cytokines that promote inflammation, such as TNF-α, IFN-γ, IL-6, and IL-1β. Additionally, by lowering the expression of inflammatory mediators such phosphorylated p65, phosphorylated IκBα, iNOS, and COX-2, BSP-2 prevented the activation of the NF-κB signaling pathway. Interestingly, BSP-2 promoted macrophage proliferation at higher concentrations while exhibiting anti-inflammatory effects under inflammatory conditions. These findings suggest that

BSP-2 possesses significant immunomodulatory and anti-inflammatory activities, [73].

2.2. Dryopteris cochleate

Family: Polypodiaceae

Dryopteris cochleate, also known as Dryopteris cochleata, is a native fern of Asia and India that belongs to the Dryopteridaceae family. This perennial herb has a strong rhizome and is frequently referred to as the Indian male fern. It is well-known for its pharmacological and ethnomedical qualities, particularly its anti-inflammatory, antibacterial, and antioxidant qualities [74]. Patil et al. (2026) developed liposomes loaded with Dryopteris cochleata extract and evaluated their immunostimulatory activity in male Wistar albino rats. In an acute toxicity trial conducted prior to efficacy investigations, the extract showed safety at an oral dose of 2000 mg/kg. The carbon clearance assay, a reliable method for assessing innate immune responses and phagocytic function, was used to measure immunomodulatory activity. The reticuloendothelial system was stimulated in the animals treated with D. cochleata extract and extract-loaded liposomes, as evidenced by considerably higher phagocytic indices as compared to the control group. The phagocytic index increased roughly 5.75 times over the control, compared to 3.14 times for the extract alone, while the typical immunostimulant levamisole produced a 7.5-fold increase. The liposomal formulation generated a stronger immunostimulatory response than the crude extract. The increased stability, bioavailability, and cellular uptake of phytoconstituents including flavonoids and phenolic compounds were thought to be responsible for the liposomal formulation's increased action. Additionally, the improved liposomes demonstrated excellent antioxidant activity, outstanding colloidal stability, and a particle size of roughly 147.5 nm. These results imply that the immunotherapeutic potential of D. cochleata and other medicinal plants for the treatment of infectious diseases, immunodeficiency disorders, and chronic inflammatory disorders can be enhanced through liposomal encapsulation [75].

2.3. Baccharis dracunculifolia

Family: Asteraceae

Baccharis dracunculifolia is a prominent medicinal shrub native to South America. It is widely used in traditional medicine for its anti-inflammatory, antioxidant, and liver-protecting properties. Ecologically, it is the primary botanical source from which bees collect resin to produce green Brazilian propolis, has demonstrated significant immunomodulatory potential [76]. Phytochemical analysis revealed the presence of diverse bioactive constituents, including polyphenols, flavonoids, terpenoids, polysaccharides, and cinnamic acid derivatives. In vitro investigations showed that the hydroethanolic extract was non-cytotoxic and modulated immune responses through activation of Toll-like receptor 4 (TLR-4) and key intracellular signaling pathways, including MAPK, ERK1/2, and NF-κB. The extract also influenced the production of several cytokines, such as IL-6, IL-2, IL-1β, IL-10, and TNF-α, indicating its ability to regulate both innate and adaptive immune responses. Furthermore, bioinformatic and network pharmacology analyses supported the involvement of multiple molecular targets associated with immune regulation. These findings highlight the immunomodulatory activity of B. dracunculifolia and suggest its potential as a promising natural agent for the development of immune-supportive therapeutics and functional health products [77].

2.4. Codonopsis pilosulae

Family: Campanulaceae

Codonopsis pilosula is an herbaceous perennial climbing vine indigenous to East and Central Asia. It is also commonly referred to as "poor man's ginseng" or "Dang Shen." Its dried roots are highly valued in Asian herbalism and are frequently used as a dietary remedy to strengthen the immune system and increase vitality [78]. the polysaccharides have attracted considerable attention due to their significant immunomodulatory properties. Purified polysaccharide fractions isolated from different varieties of *C. pilosula* were structurally characterized as fructan-type polysaccharides predominantly composed of fructose with small amounts of glucose. In vivo studies using an immunocompromised

zebrafish model demonstrated that these polysaccharides exhibited potent immunostimulatory effects by enhancing neutrophil and macrophage populations while lowering pro-inflammatory cytokine levels, such as IL-6, IL-1, and TNF-α. The immunomodulatory activity was found to be dose-dependent and appeared to be influenced by structural characteristics including glycosidic linking patterns, branching degree, and molecular weight. These findings suggest that C. pilosula polysaccharides possess promising immune-regulating potential and may serve as valuable natural ingredients for the development of functional foods, nutraceuticals, and immunotherapeutic agents [79].

2.5. Lonchocarpus cultratus

Family: Fabaceae

Lonchocarpus cultratus, a fast-growing, semideciduous tree in the legume family (Fabaceae), is sometimes referred to as embira or embira-de-sapo in Brazil. It is indigenous to South America and is mostly utilized in natural medicine, heavy metal phytoremediation, and ecological restoration. a medicinal plant rich in bioactive compounds, particularly chalcones, polyphenols, and alkaloids, which contribute to its immunomodulatory potential [80]. In the study, hexane, dichloromethane, and methanolic seed extracts were evaluated through in vitro assays for cytotoxicity, antileishmanial activity, nitric oxide (NO) production, and antioxidant capacity. The extracts demonstrated significant inhibitory effects against Leishmania amazonensis promastigote and amastigote forms, with the hexane and dichloromethane extracts showing the highest activity. Additionally, all extracts reduced NO production in lipopolysaccharide-stimulated macrophages, indicating anti-inflammatory and immunomodulatory effects. Antioxidant assays confirmed effective free radical scavenging activity, particularly in the hexane extract. The biological activities were attributed to the synergistic action of chalcones and other phytochemicals. These findings suggest that L. cultratus possesses promising immunomodulatory, antioxidant, and antiparasitic properties with potential therapeutic applications [81].

2.6. Bidens pilosa L.

Family: Asteraceae

Bidens pilosa L., a global annual herb in the Asteraceae family, is often referred to as blackjack, Spanish needles, or cobbler's pegs. It is a highly prized medicinal and delicious plant with more than 40 traditional and scientifically proven bioactivities, and it is widely acknowledged as a pioneer weed [82]. Ethyl acetate extract (BPA), rich in flavonoids and polyacetylenes, has demonstrated significant immunomodulatory and anticancer activities. In this study, BPA and its major constituents were evaluated using in vitro assays involving macrophages, regulatory T cells (Tregs), flow cytometry, qRT-PCR, and RNA sequencing, followed by in vivo assessment in a murine colorectal cancer model. The results showed that BPA selectively inhibited the differentiation of immunosuppressive M2 tumor-associated macrophages and Tregs without affecting M1 macrophages. BPA also restored $CD4^+$ T-cell proliferation, reduced the expression of immunosuppressive cytokines and markers, and enhanced antitumor immune responses. In mice, BPA significantly suppressed tumor growth, decreased serum IL-10 levels, and reduced tumor cell proliferation without causing notable toxicity. Mechanistic studies revealed modulation of NF-κB, IL-17, and cytokine-related signaling pathways. These findings highlight B. pilosa as a promising natural immunomodulator with potential applications in cancer immunotherapy [83].

2.7. Ziziphus jujuba

Family: Rhamnaceae

Ziziphus jujuba, often called the Chinese date, red date, or jujube, is a very hardy deciduous tree or shrub that is a member of the buckthorn family (Rhamnaceae). It originated in China and has been cultivated for more than 4,000 years. It is highly valued for its many traditional medicinal purposes as well as its wonderful edible fruit [84]. Polysaccharides isolated from "*Huizao" jujube (Ziziphus jujuba*) exhibited significant immunomodulatory activity in both in vitro and in vivo studies. The purified polysaccharide fraction, HP2-1, was obtained through DEAE-cellulose and Sephadex G-100 chromatography and evaluated using

RAW264.7 macrophages and cyclophosphamide-induced immunosuppressed mice. HP2-1 significantly enhanced macrophage viability, phagocytic activity, reactive oxygen species production, and the secretion of immune mediators, including nitric oxide, IL-1β, TNF-α and IL-6. In immunosuppressed mice, HP2-1 improved spleen histology, increased serum IgA and IgM levels, elevated antioxidant enzyme activities (SOD, CAT, and GSH-Px), and reduced oxidative stress. Mechanistic investigations demonstrated that HP2-1 activated the TLR4/MAPK/NF-κB signaling pathway by enhancing the expression of TLR4 and phosphorylation of ERK, JNK, p38, and NF-κB. These findings suggest that jujube polysaccharides are promising natural immunomodulators with potential applications in functional foods and immune-supportive therapeutics [85].

2.8. *Flourensia cernua*

Family: Asteraceae

Flourensia cernua (F. cernua), commonly known as American tarwort or Tarbush, is a resilient, resinous shrub indigenous to the southwestern United States and northern Mexico's Chihuahuan desert. Widely referred to in Mexican traditional medicine as hojasén or hojasé, the plant is noted for its aromatic, medicinal properties. it's a medicinal plant rich in bioactive polyphenols, including caffeic acid, apigenin, myricetin, and quercetin, which exhibit promising regenerative and immunomodulatory properties [86]. In this work, fermented *F. cernua* extracts were incorporated into collagen hydrogels to develop sustained-release bioactive scaffolds for tissue regeneration. Physicochemical characterization demonstrated enhanced hydration, crosslinking density, thermal stability, and controlled release of the extract, particularly in hydrogels containing 14 wt.% extract. Biological evaluation revealed excellent hemocompatibility without erythrocyte lysis and significant stimulation of fibroblast and monocyte proliferation. Hydrogels containing 7 weight percent extract showed anti-inflammatory efficacy by lowering TNF-α production, while those loaded with 14 wt.% extract promoted cellular metabolic activity and accelerated wound closure, achieving approximately 90% contraction within 10 days. These results imply that collagen hydrogels loaded with F. cernua have significant promise as multipurpose biomaterials for tissue regeneration, wound healing, and immunological regulation [87].

2.9. *Siraitia grosvenorii*

Family: Cucurbitaceae

Siraitia grosvenorii, an herbaceous perennial vine indigenous to southern China, is also referred to as monk fruit or Luo Han Guo. a member of the Cucurbitaceae (gourd) family, Studies indicate the fruit's phytochemicals possess antioxidant, anti-inflammatory, and immune-modulating. Siraitia grosvenorii polysaccharides have shown encouraging immunomodulatory and antioxidant qualities [88]. This work used hot water, acid-assisted, alkaline-assisted, enzyme-assisted, and ultrasonic-assisted extraction techniques to extract five polysaccharide fractions (SGP-H, SGP-A, SGP-B, SGP-E, and SGP-U). Significant variations in the fractions' surface appearance, glycosidic bonds, molecular weight, and monosaccharide composition were found through structural characterisation. Among them, SGP-B, which was extracted with alkaline assistance, had the lowest uronic acid level and a distinct glucose-rich makeup. According to biological analysis, SGP-B had the highest antioxidant activity and the best ability to scavenge DPPH and ABTS radicals. Additionally, SGP-B dramatically increased phagocytic activity and boosted the release of immune-related proteins, according to immunomodulatory tests utilizing RAW264.7 macrophages. These results imply that S. grosvenorii polysaccharides, especially SGP-B, are intriguing natural immunomodulators and antioxidants with prospective uses in immune-supportive medicines and functional foods [89].

2.10. *Ficus hirta*

Family: Moraceae

Ficus hirta, a commonly used shrub to small tree in the mulberry/fig family (Moraceae), is also referred to as the Hairy Fig or East-Indian Hairy Fig. Due to its unique flavour and therapeutic qualities, this native of tropical and subtropical Asia is widely used in everyday cuisine as well as traditional ethnobotany [90]. The methods of hot water extraction (HWE), ultrasound-assisted extraction (UAE), enzymatic-assisted extraction (EAE), and fermentation-assisted

extraction (FAE) were used in this investigation to extract polysaccharides. and their physicochemical characteristics and biological activities were compared. The extracted polysaccharides exhibited significant differences in extraction yield, monosaccharide composition, molecular weight distribution, and structural features. HWE-FHVP and FAE-FHVP showed superior water and oil absorption capacities, while EAE-FHVP demonstrated enhanced emulsifying properties. Antioxidant evaluation revealed that UAE-FHVP possessed the strongest DPPH and ABTS free radical scavenging activity. In contrast, HWE-FHVP and FAE-FHVP exhibited notable immunostimulatory effects by significantly enhancing immune enzyme secretion in RAW264.7 macrophages. These findings indicate that F. hirta polysaccharides possess valuable antioxidant and immunomodulatory activities, with their functional properties strongly influenced by the extraction method employed [91].

CONCLUSION

Conventional pharmacological approaches to immunomodulation involve the use of agents that either suppress or stimulate immune responses to maintain immune balance and treat immune-related disorders. Immunosuppressive drugs, including glucocorticoids, cyclosporine, tacrolimus, sirolimus, azathioprine, and cyclophosphamide, are widely used in organ transplantation, autoimmune diseases, and inflammatory conditions. These agents act through various mechanisms, such as inhibiting lymphocyte activation, cytokine production, and cellular proliferation. Biologic therapies, including monoclonal antibodies and cytokine inhibitors, provide targeted immune regulation by blocking specific immune pathways. Immunostimulants, such as levamisole, interferons, and cytokine-based therapies, enhance immune cell activity, cytokine production, and host defense mechanisms, making them useful in immunodeficiency disorders, infections, and cancer therapy. Although these pharmacological agents have significantly improved disease management and patient outcomes, their long-term use is often associated with adverse effects, including nephrotoxicity, hepatotoxicity, increased susceptibility to infections, and metabolic disturbances. Consequently, there is growing interest in developing safer and more selective immunomodulatory therapies, including plant-derived bioactive compounds, to achieve effective immune regulation with reduced side effects.

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