REVIEW ARTICLE

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Natural Immunostimulan for Immune Modulation: Evidence from Experimental Studies and Clinical Application

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Immune dysfunction, often triggered by stress, chronic illness, or environmental factors, underscores the urgent need for effective immunotherapeutic strategies. Natural immunostimulants have gained attention as promising agents to strengthen host defense, particularly when immunity is compromised. The research gap in this context lies in the limited understanding of the specific mechanisms by which natural immunostimulants interact with the immune system, particularly when immunity is compromised. A total of 85 studies published between 2015 and 2025 were reviewed, focusing on experimental and clinical research of natural products with immunostimulatory effects, excluding reviews, case reports, and non-English articles. Findings indicate that plant, fungal, and animal-derived immunostimulants enhance immunity by activating innate and adaptive responses, modulating cytokine networks, and stimulating natural killer cell activity. Representative examples include *Echinacea* spp., *Aloe vera*, *Withania somnifera*, medicinal fungi, and bee-derived products. These agents demonstrate therapeutic potential in infection prevention, cancer immunotherapy, vaccine adjuvantation, and immune recovery. In conclusion, natural immunostimulants offer practical benefits for enhancing immune resilience and supporting conventional therapies. However, future research should emphasize standardized formulations, dose–response relationships, and well-designed clinical trials to establish efficacy and safety in diverse populations.

Keywords: immunomodulator, immunostimulant, immunostimulant effectiveness, immune modulation, immune system

Introduction

The immune system represents one of the most sophisticated and intricate biological networks in human physiology, serving as the primary defense mechanism against a vast array of pathological threats including infectious agents, malignant transformations, and foreign substances.[1-3] This multifaceted system encompasses both innate and adaptive immunity, orchestrating a complex interplay between cellular and humoral components to maintain homeostasis and protect the host from internal and external challenges.[4] The innate immune system provides immediate, non-specific responses through physical barriers, cellular defenders such as macrophages and neutrophils, and molecular mediators including complement proteins and cytokines.[5] Simultaneously, the adaptive immune system develops highly specific, memory-based responses through T and B lymphocytes, enabling long-term protection and enhanced responses upon re-exposure to previously encountered antigens.

Despite its complexity, the immune system is vulnerable to dysfunction. A variety of factors can weaken

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immune competence, including chronic stress that elevates cortisol and suppresses lymphocyte activity,[1] nutritional deficiencies that impair immune cell function,[2] and chronic diseases such as diabetes or cardiovascular disorders that sustain inflammation.[3] Environmental exposures (pollutants, radiation, toxins) and unhealthy lifestyles (poor sleep, alcohol, inactivity) further accelerate immune decline.[4] Impaired immunity increases susceptibility to infections, reduces vaccine efficacy, delays wound healing, and raises cancer risk.[4-6] It may also drive chronic inflammation, autoimmune conditions, and allergies, underscoring the need for comprehensive therapeutic strategies.[6]

In response to these challenges, the field of immunomodulation has emerged as a promising therapeutic strategy.[7] Immunostimulants, a specialized subset of immunomodulatory agents, are defined as substances that enhance or restore immune function when compromised.[8] They act through mechanisms such as immune cell activation, increased cytokine production, antibody stimulation, and improved cellular responses.[9] Their therapeutic potential spans infection prevention and treatment, improved vaccine efficacy, and support for cancer immunotherapy.[10,11] The field of immunostimulant research includes both synthetic drugs and natural agents. While synthetic compounds show clinical efficacy, their use is limited by high cost, side effects, and limited accessibility.[12-14] These challenges have renewed interest in natural immunostimulants, valued for their lower cost, broader availability, favorable safety, and multitarget effects from complex phytochemical compositions.[13]

Natural immunostimulants are derived from diverse sources such as plants, fungi, marine organisms, and microbes.[15] Plant-based compounds polysaccharides, alkaloids, phenolics, saponins, and essential oils modulate immunity through different pathways. Fungal β-glucans are particularly noted for strong immune activation[16,17], while marine and microbial products provide novel bioactive scaffolds.[13] Evidence shows these agents act through innate and adaptive immune pathways, including toll-like receptor signaling, complement activation, cytokine modulation, and immune cell stimulation.[18,19] Clinically, natural immunostimulants are applied in infection prevention, vaccine response enhancement, cancer therapy support, chronic inflammation management, and immune recovery in compromised individuals.[20]

Despite extensive research, natural immunostimulants face challenges in clinical translation, including standardization of extracts, identification of active compounds, dosing optimization, long-term safety assessment, and regulatory approval.[8,12,13,21] Their complex phytochemical nature also complicates the precise characterization of mechanisms. Importantly, although many studies report immune-enhancing effects, few comprehensive reviews integrate mechanisms, natural sources, and clinical applications in a unified framework.

This narrative review addresses this gap by critically evaluating current evidence on natural immunostimulants. It explores their mechanisms of action, therapeutic potential across diverse clinical contexts, and the strength of supporting data. In addition, it highlights translational challenges, identifies research gaps, and outlines future directions to advance their development. By synthesizing available findings, this review aims to guide researchers, clinicians, and policymakers in understanding the potential role of natural immunostimulants in strengthening human health and disease prevention.

Methods

The literature included in this review was identified through systematic searches on databases such as Google Scholar, ScienceDirect, ResearchGate, and BMC. The keywords used included "immunomodulator," The search was limited to original research articles published between 2015 and 2025 that investigated the immunostimulatory effects of natural compounds, including both *in vitro* and *in vivo* studies. An initial screening of 1,240 records was conducted from databases such as PubMed, ScienceDirect, and Google Scholar. After removing duplicates, reviews, case reports, and articles lacking primary experimental or clinical data, 85 studies met the inclusion criteria and were analyzed in this review. Focusing solely on synthetic immunostimulants, reviews, and unrelated pharmacological activities were excluded to maintain the focus on natural immunostimulants with demonstrated immunomodulatory activities.[17]

Results

Immunomodulatory Mechanism and Enhancement of Innate Immune Responses by Natural Compounds

Natural immunostimulants exert their therapeutic efficacy by modulating multiple immune components through diverse mechanisms, often displaying pleiotropic effects on

both innate and adaptive responses.[20,22,23] A key target is the innate immune system, the first line of defense that provides rapid, non-specific protection.[24] These compounds enhance the activity of professional phagocytes such as macrophages, neutrophils, and dendritic cells, thereby improving pathogen recognition, elimination, and antigen presentation.[23,24]

Macrophages show significant functional enhancement when exposed to plant-derived compounds. For example, *Allium sativum* (garlic) contains allicin and other organosulfur molecules that boost phagocytic activity, increase reactive oxygen species (ROS) and nitric oxide production, and enhance pathogen clearance via improved receptor expression and phagosome-lysosome fusion.[23,25] Similary, polysaccharides from Plantago major act as pathogen-associated molecular pattern (PAMP) mimics, activating toll like receptors (TLRs) and triggering antimicrobial peptide release, oxidative burst, and M1 macrophage polarization, thereby strengthening antimicrobial and antitumor functions.[19,23,25]

Neutrophils are similarly stimulated by alkaloids from Alstonia scholaris, which promote chemotaxis, degranulation, respiratory burst, and neutrophill extracellular traps (NET) formation.[26,27] This leads to prolonged neutrophil survival and increased bactericidal capacity through elevated myeloperoxidase and hypochlorous acid production, making them more effective against bacterial pathogens.[26,28]

Stimulation of Adaptive Immunity

The adaptive immune system provides highly specific, memory-based responses that form the foundation of long-term immunity and vaccine efficacy.[24] Natural immunostimulants demonstrate remarkable ability to enhance various aspects of adaptive immunity, particularly through the stimulation of lymphocyte proliferation, differentiation, and effector functions[29]. This enhancement is crucial for developing robust immune memory and ensuring effective responses to subsequent pathogen encounters.[25]

A. vera, a succulent plant renowned for its medicinal properties, contains a complex mixture of bioactive compounds including acemannan, aloin, and various polysaccharides that exhibit potent immunostimulatory effects on adaptive immunity.[25] Research has demonstrated that *Aloe vera* extracts significantly enhance B lymphocyte proliferation and differentiation into plasma cells, leading to increased production of immunoglobulins, particularly immunoglobulin G (IgG) and immunoglobulin M (IgM).[27] The mechanism involves activation of B cells through complement receptor signaling and enhanced antigen presentation by dendritic cells.[25,30] Additionally, *A. vera* compounds promote T helper cell activation and cytokine production, creating a favorable microenvironment for antibody class switching and affinity maturation.

Blumea balsamifera demonstrates similar immunostimulatory properties through its rich content of flavonoids, terpenoids, and phenolic compounds.[30] These bioactive molecules enhance lymphocyte activation by modulating cell surface receptor expression and intracellular signaling pathways. Studies have shown that *B.balsamifera* extracts increase the expression of CD40 ligand on T helper cells, which is essential for providing costimulatory signals to B cells.[30] This enhanced T-B cell interaction results in improved germinal center formation, increased somatic hypermutation, and enhanced production of high-affinity antibodies.[30] The stimulation also extends to memory cell formation, ensuring long-lasting protective immunity.[6]

Mangifera indica (mango) extracts, particularly those derived from leaves and bark, contain mangiferin, gallic acid, and other polyphenolic compounds that demonstrate significant immunostimulatory effects on adaptive immunity. These compounds enhance T lymphocyte proliferation and activation, leading to increased production of effector T cells and regulatory T cells.[26,30] The balanced stimulation of different T cell subsets is crucial for maintaining immune homeostasis while ensuring effective pathogen clearance. Research has shown that *M. indica* extracts promote the development of Th1 responses, which are essential for cell-mediated immunity against intracellular pathogens, while simultaneously supporting humoral immunity through enhanced B cell activation and antibody production.[30]

Cytokine Modulation

Cytokines serve as the primary communication molecules of the immune system, orchestrating complex interactions between different immune cell populations and regulating the magnitude and duration of immune responses.[31] Natural immunostimulants demonstrate sophisticated ability to modulate cytokine networks, ensuring balanced and effective immune responses while preventing excessive inflammation or immunopathology as shown in **Figure 1**.[8,32]

Zingiber officinale (ginger) contains bioactive compounds including gingerols, shogaols, and zingerone that exhibit complex immunomodulatory effects on cytokine production.[24] Research has demonstrated that ginger extracts

can selectively enhance the production of pro-inflammatory cytokines such as interleukin 2 (IL-2), tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ) when immune stimulation is required, while simultaneously promoting the production of anti-inflammatory cytokines such as IL-10 and TGF-β to prevent excessive inflammation.[31,33] This dual modulatory capacity is achieved through differential activation of transcription factors including NF-κB, activator protein-1 (AP-1), and signal transducer and activator of transcription (STAT) proteins, which regulate cytokine gene expression.[9] The balanced cytokine response promoted by ginger extracts ensures effective pathogen clearance while minimizing tissue damage and chronic inflammation.

Nigella sativa (black cumin) seeds contain thymoquinone, nigellone, and other bioactive compounds that demonstrate potent immunomodulatory effects on cytokine networks.[23,34] Studies have shown that *N. sativa* extracts enhance IL-2 production by T helper cells, which is crucial for T cell proliferation and activation.[23] Simultaneously, these extracts modulate IL-6 production, ensuring appropriate acute phase responses without promoting chronic inflammation.[18] The modulation of TNF-α production by *N. sativa* is particularly noteworthy, as this cytokine plays dual roles in immune activation and inflammation. The extracts enhance TNF-α production during acute immune responses while preventing excessive production that could lead to tissue damage.[23]

Cymbopogon flexuosus (lemongrass) essential oils contain citral, geraniol, and other terpenes that demonstrate unique immunomodulatory properties through cytokine regulation.[35-37] Research has revealed that lemongrass extracts enhance IFN-γ production by T helper 1 cells and natural killer cells, promoting antiviral and antitumor immunity.[35] The enhanced IFN-γ production is accompanied by increased IL-12 production by dendritic cells and macrophages, creating a positive feedback loop that promotes cell-mediated immunity.[36] Additionally, lemongrass extracts modulate the production of chemokines, ensuring appropriate immune cell recruitment to sites of infection or injury.

NK Cell Activation and Immune Surveillance

Natural killer (NK) cells represent a unique population of lymphocytes that bridge innate and adaptive immunity, providing rapid responses against virally infected cells and tumor cells without requiring prior sensitization.[17,29] The enhancement of NK cell activity by natural immunostimulants represents a crucial mechanism for improving immune surveillance and preventing malignant transformation and viral persistence.[15]

Panax ginseng (Asian ginseng) contains ginsenosides, polysaccharides, and other bioactive compounds that demonstrate remarkable ability to enhance NK cell function.[41] Research has shown that ginseng extracts increase NK cell cytotoxicity through multiple mechanisms including enhanced perforin and granzyme production, improved degranulation capacity, and increased expression of activating receptors such as natural killer group 2D (NKG2D) and natural killer protein 46 (NKp46).[39] The enhanced NK cell activity results in improved recognition and elimination of stressed, infected, or transformed cells.[42] Additionally, ginseng extracts promote NK cell proliferation and survival, ensuring sustained immune surveillance capacity.[38,39] The immunostimulatory effects extend to enhancing NK cell memory-like responses, which provide improved protection against recurring infections.

Echinacea species, particularly *E. purpurea, E. angustifolia*, and *E. pallida*, contain alkamides, caffeic acid derivatives, and polysaccharides that demonstrate potent NK cell stimulatory propertis.[14,33,40,41] Studies have revealed that *Echinacea* extracts enhance NK cell activation through multiple pathways including increased expression of activation markers, enhanced cytokine production (particularly IFN-γ and TNF-α), and improved cytolytic function.[14,33] The enhanced NK cell activity is accompanied by increased antibody-dependent cellular cytotoxicity (ADCC), which is crucial for eliminating antibody-coated target cells.[33] Furthermore, *Echinacea* extracts promote NK cell trafficking to sites of infection or tumor development, ensuring efficient immune surveillance throughout the body.

The enhancement of NK cell function by natural immunostimulants has significant therapeutic implications for cancer prevention and treatment, as well as for controlling viral infections.[42] The improved immune surveillance capacity helps prevent malignant transformation of normal cells and enhances the elimination of existing tumor cells. Additionally, enhanced NK cell activity contributes to controlling viral infections, particularly those caused by enveloped viruses that are susceptible to NK cell-mediated cytotoxicity. The sustained enhancement of NK cell function by natural immunostimulants provides a foundation for long-term immune protection and improved overall immune competence.

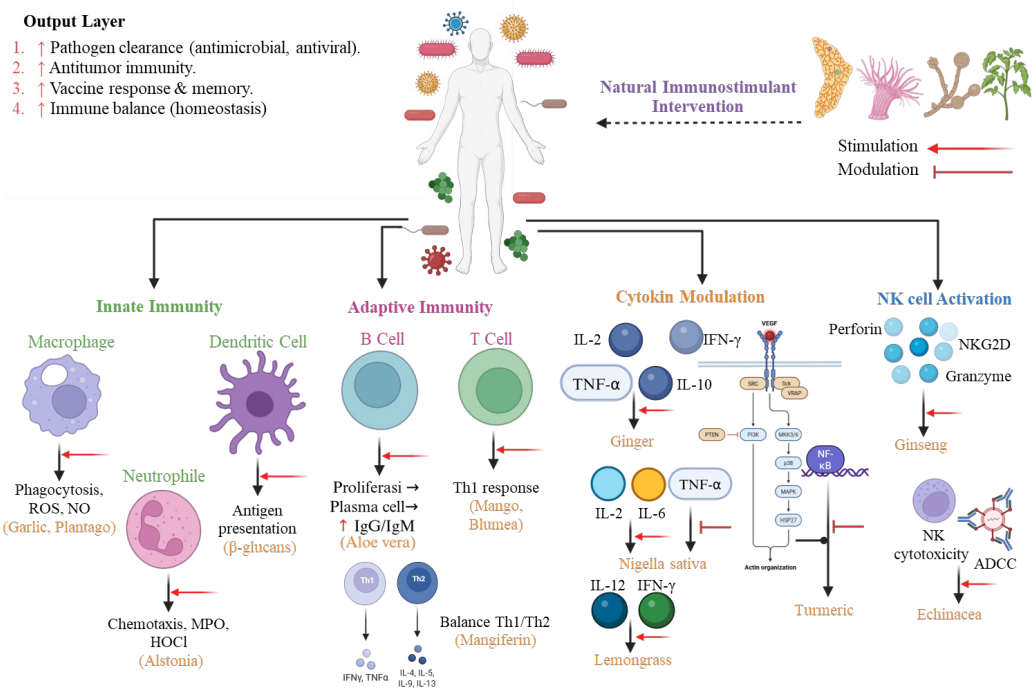

Figure 1. Mechanistic overview of natural-derived immunostimulants against pathogen infection.

Plant-Derived Immunostimulants

Medicinal plants have been extensively studied for their immunomodulatory activities, with research consistently demonstrating their remarkable capacity to enhance immune system function through diverse molecular mechanisms.[46] The therapeutic potential of plant-derived immunostimulants stems from their complex phytochemical compositions, which often contain multiple bioactive compounds working synergistically to modulate both innate and adaptive immune responses.[47] This multi-target approach provides significant advantages over single-compound synthetic drugs, offering broader therapeutic effects with reduced risk of adverse reactions and drug resistance.

The immunomodulatory properties of medicinal plants are primarily attributed to specific classes of bioactive compounds, each demonstrating distinct mechanisms of action and therapeutic applications.[44] Flavonoids and terpenoids represent two of the most extensively studied compound classes, with numerous plants containing these phytochemicals showing significant immunostimulatory effects.[44] *Phyllanthus niruri*, commonly known as stone breaker, contains a diverse array of flavonoids including quercetin, kaempferol, and rutin, alongside terpenoids and lignans such as phyllanthin and hypophyllanthin.[45] These compounds work synergistically to enhance immune cell function through multiple pathways, including increased T lymphocyte proliferation, enhanced macrophage activation, and improved antigen presentation. The plant's flavonoids demonstrate potent antioxidant properties that reduce oxidative stress-induced immune dysfunction, while simultaneously promoting the production of key cytokines necessary for effective immune responses.[46]

Echinacea species, particularly *E. purpurea*, *E. angustifolia*, and *E. pallida*, represent paradigmatic examples of terpenoid-rich immunostimulants that have been extensively validated through clinical research.[14,33,45] The immunomodulatory effects of *Echinacea* are attributed to its complex phytochemical profile, which includes terpenoids such as echinacoside and chicoric acid, alkamides, polysaccharides, and caffeic acid derivatives.[33] These compounds demonstrate preferential effects on innate immunity, particularly through activation of macrophages, dendritic cells, and natural killer cells. Research has shown that Echinacea extracts can enhance macrophage phagocytic activity by up to 40%, while simultaneously increasing the production of crucial cytokines including interleukin-1β, tumor necrosis factor-α, and interleukin-6.[45] The clinical applications of *Echinacea* preparationshave been extensively investigated in randomized controlled trials, with meta-analyses indicating significant benefits for respiratory tract

infection prevention and treatment, demonstrating effect sizes comparable to conventional pharmaceutical interventions.

Withania somnifera (ashwagandha) represents a unique category of plant-derived immunostimulants known as adaptogens, which demonstrate the ability to enhance stress resistance while modulating immune function. The plant's immunomodulatory properties are primarily attributed to withanolides, a group of naturally occurring steroids including withanoside IV, withanoside VI, and withanolide D, working in conjunction with flavonoids and phenolic compounds. The adaptogenic properties of *W. somnifera* are particularly relevant for immune function, as chronic stress represents a major factor in immune suppression and increased disease susceptibility.[47] Clinical studies have demonstrated that standardized. *W. somnifera* extracts can reduce serum cortisol levels by up to 30% in chronically stressed individuals, with corresponding improvements in immune parameters including increased natural killer cell activity and enhanced antibody production.[47] The plant's compounds exhibit unique immunomodulatory properties that enhance immune function in both immunocompromised and immunocompetent individuals, while simultaneously preventing excessive immune activation through their anti-inflammatory effects.

Curcuminoids and gingerols represent another significant class of plant-derived immunomodulatory compounds, distinguished by their ability to modulate specific immune signaling pathways with remarkable precision.[23,33,48] *Curcuma longa* (turmeric) and its primary bioactive compound curcumin demonstrate potent immunomodulatory effects primarily through their ability to modulate key inflammatory signaling pathways, particularly nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK) cascades.[48] Curcumin demonstrates remarkable ability to inhibit NF-κB activation through multiple mechanisms, including direct interaction with the IκB kinase complex, prevention of IκBα phosphorylation and degradation, and interference with NF-κB nuclear translocation. This multi-target approach ensures comprehensive modulation of NF-κB-dependent gene expression, resulting in balanced inflammatory responses that maintain protective immunity while preventing excessive inflammation.[23,48] The therapeutic applications of curcumin in immune-related disorders have been extensively investigated in clinical trials, with meta-analyses indicating that curcumin supplementation significantly reduces inflammatory markers including C-reactive protein, interleukin-6, and tumor necrosis factor-α, while improving clinical outcomes in various inflammatory conditions.

Z. officinale (ginger) contains a diverse array of bioactive compounds, with gingerols, shogaols, and zingerone representing the primary immunomodulatory constituents.[23] These compounds demonstrate complex immunomodulatory properties through modulation of multiple signaling pathways, including NF-κB, MAPK, and cyclooxygenase pathways, resulting in comprehensive immune system modulation. The gingerols in *Z. officinale* demonstrate unique immunomodulatory properties that distinguish them from other plant-derived anti-inflammatory compounds, exhibiting context-dependent immunomodulation that enhances immune responses when stimulation is needed while suppressing excessive inflammatory responses when inflammation becomes harmful. Recent investigations have revealed that 6-gingerol, the predominant active compound, demonstrates significant capacity to enhance dendritic cell function and antigen presentation, improving the initiation of adaptive immune responses through increased expression of major histocompatibility complex class II molecules and costimulatory molecules on dendritic cells.[23,48]

Fungal-Derived Immunostimulants

Fungal-derived immunostimulants represent a distinct and highly potent category of natural bioactive compounds, with β-glucans emerging as the most extensively studied and clinically validated fungal immunomodulators.[16,17] These complex polysaccharides, characterized by their unique structural configurations and molecular weights, demonstrate remarkable immunostimulatory properties that have positioned them as valuable therapeutic agents in both preventive and therapeutic applications. The immunomodulatory effects of fungal β-glucans are primarily attributed to their ability to interact with specific immune receptors, particularly complement receptor 3 (CR3), dectin-1, and toll-like receptors, initiating robust immune responses that enhance both innate and adaptive immunity.[16] Unlike plant-derived immunostimulants that often work through multiple phytochemical classes, fungal immunostimulants achieve their effects primarily through these structurally distinct polysaccharides, which exhibit species-specific variations in molecular structure and biological activity.[17]

Lentinula edodes (shiitake mushroom) and *Pleurotus ostreatus* (oyster mushroom) represent two of the most extensively researched fungal species for

their immunomodulatory properties, with their β-glucans demonstrating potent immunostimulatory effects across multiple immune system components.[25] The β-glucans from *L. edodes*, particularly lentinan, exhibit remarkable capacity to activate dendritic cells, enhancing their maturation, migration, and antigen-presenting capabilities, which subsequently leads to improved T cell activation and proliferation.[25,49] These compounds significantly enhance cytokine responses, promoting the production of key immunomodulatory cytokines including interleukin-12, interferon-γ, and tumor necrosis factor-α, while simultaneously modulating the production of anti-inflammatory cytokines to maintain immune homeostasis.

The β-glucans from *Pleurotus ostreatus* demonstrate similar immunostimulatory properties, with additional effects on natural killer cell activation and macrophage function, contributing to enhanced immune surveillance and pathogen elimination.[49,50] The clinical applications of these fungal β-glucans have been extensively investigated, with established roles in cancer adjuvant therapy where they enhance the efficacy of conventional treatments, improve patient survival rates, and reduce treatment-associated side effects.[49] Their ability to simultaneously enhance immune responses against tumor cells while modulating inflammatory responses has made them valuable components in integrative cancer treatment protocols, with numerous clinical trials demonstrating their safety and efficacy in various cancer types including gastric, colorectal, and hepatocellular carcinomas.

Other Sources of Immunostimulants

Beyond plant and fungal sources, diverse biological origins contribute to the expanding repertoire of natural immunostimulants, with compounds derived from bee products, marine organisms, and other animal sources demonstrating significant immunomodulatory properties. Royal jelly, a proteinaceous secretion produced by honeybee worker glands, contains a complex mixture of bioactive compounds including major royal jelly proteins (MRJPs), fatty acids, adenosine compounds, and various peptides that exhibit potent immunostimulatory effects.[28] The immunomodulatory properties of royal jelly are primarily attributed to its ability to enhance immune cell proliferation and differentiation, particularly promoting the development of regulatory T cells and enhancing antibody production by B lymphocytes.[28]

Research has demonstrated that royal jelly compounds can significantly increase the proliferation of peripheral blood mononuclear cells, enhance natural killer cell activity, and improve the phagocytic capacity of macrophages, contributing to overall immune system enhancement.[28] Honey, another bee-derived product, contains phenolic compounds, flavonoids, and various enzymes that demonstrate immunomodulatory effects primarily through anti-inflammatory actions and antioxidant properties. The immunostimulatory effects of honey are mediated through its ability to modulate cytokine production, reduce oxidative stress in immune cells, and enhance wound healing processes through improved immune cell recruitment and activation.[28,50]

Marine organisms represent an emerging and promising source of novel immunostimulant compounds, with shark cartilage being among the most extensively studied marine-derived immunomodulators. Shark cartilage contains unique glycosaminoglycans, particularly chondroitin sulfate and various sulfated polysaccharides, which demonstrate significant immunostimulatory properties through multiple mechanisms including anti-inflammatory actions and modulation of immune cell proliferation.[51] The immunomodulatory effects of shark cartilage compounds are primarily achieved through their ability to inhibit pro-inflammatory mediators while simultaneously enhancing adaptive immune responses, particularly T cell proliferation and activation.[51] Research has shown that shark cartilage extracts can significantly reduce the production of inflammatory cytokines such as interleukin-1β and tumor necrosis factor-α, while promoting the production of anti-inflammatory cytokines including interleukin-10 and transforming growth factor-β.[51]

Additionally, marine-derived compounds from various algae, sponges, and other marine organisms have shown promising immunomodulatory effects, with unique chemical structures that often exhibit novel mechanisms of action not found in terrestrial sources. These marine-derived immunostimulants demonstrate particular potential for treating chronic inflammatory conditions and autoimmune diseases, as their anti-inflammatory properties help modulate excessive immune responses while maintaining protective immunity against pathogens and malignant cells.[52]

Clinical Application and Evidence

A comprehensive literature review has enabled the identification and classification of various immunostimulant types according to their distinctive characteristics. **Table 1** until **Table 4** show illustrates the immunostimulant classification system, which categorizes these compounds based on specify the classification criteria which facilitating a systematic understanding of immunostimulant diversity and functionality.

The comprehensive literature review presented in the table reveals a diverse array of immunostimulant compounds systematically classified based on their chemical structure, biological origin, and immunomodulatory mechanisms. The classification encompasses major chemical categories including glycosides and polysaccharides (such as lentinan from *L. edodes* and mangiferin from *M. indica* alkaloids (including berberine and tetrandrine), phenolic compounds (flavonoids, tannins, and curcuminoids), and terpenoids with essential oil components (ginsenosides and withanolides). These compounds are derived from terrestrial plants, fungal sources, marine organisms, and bee products, representing a broad spectrum of natural immunoactive substances.

Functionally, these immunostimulants demonstrate diverse therapeutic profiles ranging from pure immune enhancement through increased cytokine production and phagocytic activity, to balanced immunomodulation capable of both stimulating and suppressing immune responses as needed. Many compounds exhibit pleiotropic effects, simultaneously targeting multiple immune pathways including NF-κB signaling, complement system activation, and direct immune cell stimulation. The mechanistic diversity observed includes anti-inflammatory immunomodulators that regulate excessive immune responses while maintaining protective immunity, as demonstrated by compounds from Terminalia chebula, various fruit-derived anthocyanins, and mushroom-derived β-glucans.

This systematic classification provides a comprehensive framework for understanding the therapeutic potential of natural immunostimulants in clinical applications, particularly in infectious disease management, cancer immunotherapy, vaccine adjuvant development, and general immune enhancement strategies.

Natural Immunostimulants and Application in Human Health Infectious Diseases

One of main causes cause of morbidity and mortality is infectious diseases. especially in areas with poor access to healthcare.[57] The difficulties caused by viral alterations and antibiotic resistance emphasize the necessity of supplementary approaches.[57] It has been demonstrated that natural immunostimulants improve both innate and adaptive immunity, which lowers the severity and length of illnesses.[24]

Fungal cell walls include polysaccharides called β-glucans, which are some of the most researched immunostimulants. They speed pathogen clearance by activating dendritic cells and macrophages, enhancing NK cell activity, and promoting the production of cytokines (IL-1β, IL-6, and TNF-α).[25,40,59] Through NK cell augmentation, cytokine stimulation, and macrophage activation, *Echinacea* species also have notable effects in respiratory infections; clinical investigations show a decreased incidence and shorter duration of cold symptoms. Echinacea spp. also has considerable effects on respiratory infections, operating through macrophage activation, cytokine stimulation, and NK cell augmentation; clinical trials show lower incidence and shorter symptom duration in colds and influenza.[14,35]

Other botanicals have additional benefits. *P. ginseng* boosts immune surveillance and cytokine responses, which reduces influenza-like diseases.[37,42] *N. sativa* may have antiviral effects via modulating T-cell activity and cytokines, while *C. longa* and *Z. officinale* suppress viral multiplication and inflammation by targeting NF-κB signaling.[23,34] Furthermore, substances from *Andrographis paniculata* and *Glycyrrhiza glabra* have antiviral efficacy against chronic illnesses including hepatitis and HIV.[25,43,54]

Natural Immunostimulants in Cancer Immunotherapy and Vaccine Adjuvants

Treatment of cancer is increasingly incorporating natural immunostimulants to boost antitumor immunity.[61] Lentinan, a β-glucan derived from *L. edodes*, stimulates macrophages, dendritic cells, and NK cells, leading to increased cytokine production (IL-12, IFN-γ) and improved results in gastric and colorectal cancer.[17,25,49,61] Clinical studies suggest that it improves chemotherapy efficacy and reduces immunosuppression.

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Table 1. Classification of immunomodulators from plants.

Component source	Substance	Function	Immune system response	Ref
Boerhaavia diffusa	Eupalitin-3-O- β-D-galactopyranoside	Immunosuppressive glycoside	↓ TNF-α, IL-2; ↓ PBMC proliferation	
Plantago major	Aucubin (glycoside)	Immunostimulant	↑ Lymphocyte proliferation, ↑ IFN-γ	
Urtica dioica	Isorhamnetin-3-O-glucoside	Enhances neutrophil function	↑ Intracellular killing activity	
Fumaria capreolata	Alkaloid extract	Anti-inflammatory	↓ Colitis biomarkers; modulates pro- and anti-inflammatory cytokines	
Stephania tetrandra	Tetrandrine (alkaloid)	Anti-inflammatory	↓ NF-κB, reduces microglial activation	
Hydrastis canadensis	Berberine (alkaloid)	Anti-inflammatory	↓ NO, IFN-γ, TNF-α in lung & gut inflammation	
Sinomenium acutum	Sinomenine (alkaloid)	Anti-rejection (graft model)	Prevents cardiac graft rejection	
Punica granatum	Punicalagin (tannin)	Immunosuppressive	↓ IL-2, T-cell infiltration	
Mangifera indica	Mangiferin (glycoside)	Th1/Th2 balancer, antiasthmatic	↑ IL-2, IL-10, IL-12; ↓ IL-4, IL-5, IL-13, IL-17, RANTES	
Allium cepa	Onion lectin	Immune activator	↑ NO, IL-12, TNF-α	
Terminalia chebula	Chebulagic acid, corilagin (tannins)	Immunosuppressive	↓ IL-2, TNF- α, ROS; NF- κB, p38, JNK, ERK pathway inhibition	[23]
Silybum marianum	Silymarin (flavonolignan)	Immunosuppressive	↓ CD4+ proliferation, IL-2, IFN-γ; inhibits NF-κB	
Jatropha curcas	Orientin, vitexin, apigenin variants	Immune boosting flavonoids	↑ Humoral & cell-mediated immunity in chicks	
Glinus oppositifolius	Spergulin-A (triterpenoid)	Antileishmanial, immunomodulator	Activates Th1/Th2 balance; enhances intracellular parasite killing	
Nitraria retusa	β-sitosterol (sterol)	Tumor suppressor, immune enhancer	↑ Splenocyte activity; ↓ tumor size	
Cedrus deodara	Dihydroquercetin (flavonoid)	Fish model immune booster	↑ IgM levels in seabream	
Corchorus olitorius	Water-soluble molokhia extract	Immunostimulant	↑ Leukocyte count, thymus/spleen index (mice)	
Fruits (various)	Cyanidin, delphinidin, petunidin etc. (anthocyanins)	Anti-inflammatory	↓ IL-6, TNF-α , PGE2; ↓ arthritis in rats	
Curcuma xanthorrhiza	Curcuminoid, volatile oil	Immunostimulant; enhances B and T cell responses; regulates NF- κB pathway	Elevates antibody production; regulates immune cells	
Andrographis paniculata	Terpenoids, flavonoids, alkaloids, steroids, glycosides, tannins	Immunostimulant & immunosuppressant	Increases leucocyte count, phagocytic index, enhances IgG; regulates NF-κB signaling	
Cinnamomum verum	Polyphenols, alkaloids, cinnamaldehyde, volatile oil	Anti-inflammatory	Enhances immune response in RA	
Syzygium aromaticum	Eugenol, eugenol acetate, tannins, thymol, β-caryophyllene	Enhances cytokine release	↑ IL-6, TNF- α	
Cymbopogon flexuosus	Polysaccharides	Activates T & B lymphocytes	↑ IL-2, IL-6, IL-12, TNF-α ; enhances splenocyte proliferation	
Zingiber officinale	Gingerol, shogaol, volatile oil	Modulates cytokine production	↓ IL-2, IL-10; ↑ IL-1β, IL-6, TNF-α	
Curcuma longa	Curcuminoid, volatile oil	Activates macrophages	↑ WBCs, IgG, IgM; modulates dendritic cell activity	
Phyllanthus niruri	Flavonoids, tannins, lignans	Stimulates PBMC proliferation	Enhances neutrophil and macrophage activity, NO production	[24,38,58,59]
Psidium guajava	Flavonoids, tannins, triterpenes	Stimulates humoral & cellular immunity	↑ IL-8 expression; boosts immune defense	
Piper cubeba	Piperine, piperidine, chavicine, sesquiterpenes	Immunosuppressant	↓ TNF-α, IL-6; reduces peripheral neutrophils	
Aloe vera	Carotenoids, steroids, terpenes, phytosterols	Stimulates lymphocyte proliferation	↑ IL-1β, IL-2, IL-6, TNF-α, IFN-γ	
Mangifera indica	Mangiferin	Antioxidant; humoral modulator	Enhances antibody titers; reduces oxidative stress	
Nigella sativa	Nigellone, thymol, thymohydroquinone	Proinflammatory mediator	Stimulates IL-2, IL-6, PGE2	
Carica papaya	α-Tocopherol, flavonoids, cyanogenic glycosides	Immunostimulant	↑ IgG, phagocytosis; ↓ IgM and cytokines	
Centella asiatica	Saponins, triterpenoids	Enhances immune function	↑ IgG; activates macrophages	

Table 1. Classification of immunomodulators from plants (continue).

Component source	Substance	Function	Immune system response	Ref
Camellia sinensis	EC, EGCG	Immune enhancement	↑ IL-8, IL-17A, HBD-2	
Allium sativum	Allicin, sulfur compounds	Antimicrobial, immunostimulant	Enhances macrophage activity, antibody production	
Mentha piperita	Flavonoids, phenolic acids, essential oils	Antimicrobial, anti-inflammatory	Enhances respiratory immunity	
Panax ginseng	Ginsenosides	Adaptogenic, immune-boosting	↑ IL-2, IFN-γ, NK cell activity	
Glycyrrhiza glabra	Glycyrrhizin	Anti-inflammatory, immune balancing	Modulates cytokines (IL-2, IL-4), enhances macrophages	[27,46,60]
Ocimum sanctum	Eugenol, ursolic acid	Anti-inflammatory, stress reducer	Modulates cortisol;↑ lymphocyte proliferation	
Echinacea sp.	Alkamides, caffeic acid derivatives	Immune stimulant	Stimulates macrophage phagocytosis, ↑ NK cells	
Withania somnifera	Withanolides, sitoindosides	Adaptogen, immunostimulant	Stimulates macrophages & lymphocytes	
Blumea balsamifera	Flavonoids, terpenoids, polyphenols	Anti-inflammatory	↑ Lymphocyte proliferation, antibody production, phagocytosis	[61]
Alstonia scholaris	Alkaloids, flavonoids, triterpenoids, polysaccharides	Anti-inflammatory, anti-cancer, antioxidant	Immunostimulant:↑ phagocytic index, cellular immune response	[28]
Tilia cordata	Flavonoids, mucilage, tannins, volatile oils	Anti-inflammatory, antioxidant	↑ Leukocyte & lymphocyte counts; boosts local immunity	
Thymus kotschyanus	Thymol, carvacrol, flavonoids, saponins	Antibacterial, anti-inflammatory	Enhances immune response, improves vaccine effectiveness	
Matricaria chamomilla	Apigenin, bisabolol, chamazulene	Anti-inflammatory, relaxant	Stabilizes immune system under stress	
Citrus fruits	Flavonoids, Vitamin C	Antioxidant, ACE2 inhibitor	↓ IL-1β, IL-6, TNF-α; inhibits virus entry	[62]
Kiwi	Vitamin C, carotenoids, polyphenols	Antioxidant, respiratory support	Enhances respiratory immunity,↓ symptoms	
Apple	Vitamins B2, B6, C, polyphenols	Anti-inflammatory, antioxidant	↑ T-helper, macrophages; ↓ lung inflammation	
Grapes & berries	Resveratrol, anthocyanins, quercetin	Antiviral, antioxidant	↓ IL-6, IL-8; blocks ACE2 binding	
Strawberry & blueberry	Anthocyanins, nitrates	Antioxidant, immunomodulatory	Enhances immune survival, modulates BRD4 & Nrf2	

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Table 2. Classification of Immunomodulators from Fungi

Substance	Function	Immune system response	Component source	Ref
Lentinan (β-1,3/1,6-glucan)	Anti-tumor, immunostimulant	↑ Pro-inflammatory cytokines; boosts chemotherapy efficacy	*Lentinula edodes* (Shiitake)	[32,58,65]
Pleuran (β-1,3/1,6-glucan)	Immune support, anti-fatigue	↓ Flu & respiratory infections; ↑ IL-10, ↓ IL-6	*Pleurotus ostreatus* (Oyster mushroom)	
Yestimun® (β-1,3/1,6-glucan)	Food supplement for immunity	↑ Phagocytosis, granulocyte activation	*Saccharomyces cerevisiae* (Brewer's yeast)	
Glucan #300 (83% β-glucan, oral)	Immunostimulant	No significant cytokine effect (low absorption)	*Saccharomyces cerevisiae* (Baker's yeast)	
Soluble β-1,3/1,6-glucan (IV)	Cancer immunotherapy candidate	Activates innate immune cells; cytokine release	Imprime PGG (yeast extract)	

Tabel 3. Classifiction of immunomodulators from bees.

Substance	Function	Immune system response	Component source	Ref
Flavonoids, phenolics	Immunostimulant, antioxidant	↑ Leukocytes, neutrophils, granulocytes; ↓ lymphocytes	*Tetragonula aff. biroi honey*	[36,62]
MRJP, 10-HDA	Immune-enhancing, anti-inflammatory	↑ Monocytes, suppresses IL-6 & NO, ↓ IFN-γ	Royal Jelly	

Tabel 4. Classifiction of immunomodulators from marine.

Substance	Function	Immune system response	Component source	Ref
Chondroitin sulfate, glucosamine, proteoglycans	Anti-inflammatory, anti-angiogenic, joint support	Immunostimulant: modulates CRP, uric acid, enhances immune function	*Prionace glauca* (Shark cartilage)	[63]

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Imprime PGG, a β-glucan from *Saccharomyces cerevisiae*, works through antibody-dependent processes and complement activation to improve monoclonal antibody treatments and tumor control in clinical trials.[59,62] Together, these molecules demonstrate the potential of fungal-derived immunostimulants as cancer treatment adjunct.

The efficacy of vaccines is dependent on strong and long-lasting immune responses. Natural immunostimulants are being investigated as adjuvants, particularly in vulnerable populations.[12] *W. somnifera* (ashwagandha) activates macrophages and cytokines through withanolide, leading to improved humoral and cellular responses.[47] *M. chamomilla* (chamomile) has antioxidant and moderate immunomodulatory properties that help stabilize immunological balance and boost vaccine-induced immunity.[56]

Conclusion

This review confirms that natural immunostimulants from plants, fungi, and other biological sources represent a promising frontier in immunotherapy. These agents enhance both innate and adaptive immunity through multi-target mechanisms, including cytokine regulation and antioxidant protection. Their potential applications range from infection prevention and cancer immunotherapy to vaccine adjuvantation and immune recovery, with generally favorable safety profiles and accessibility. Future research should prioritize standardization of bioactive compounds and conduct well-designed, large-scale clinical trials to validate efficacy, safety, and optimal dosing. Integrating traditional knowledge with modern approaches such as immunogenomics and immunoprofiling may further advance the development of safer, more effective, and patient-centered immunotherapies.

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Authors' Contribution

AZS conceptualized the review, performed the literature search, analyzed and synthesized the relevant studies, and wrote the original draft of the manuscript. NHQ contributed to manuscript writing and critical revisions throughout the process. K supervised the review process and revised the manuscript All authors have read and approved the final manuscript.

Conflict of Interest

The authors declare no competing interests.

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