

RECENT ADVANCES IN HERBAL IMMUNOMODULATORS AND THEIR RELEVANCE IN IMMUNITY ENHANCEMENT AND CANCER CONTROL

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Abstract

The immune system serves as the body's defense against infections and diseases. With growing concerns over antibiotic resistance and emerging pandemics, herbal immunomodulators are gaining attention as natural alternatives for enhancing immunity. These medicinal herbs, rich in bioactive compounds like flavonoids and alkaloids, modulate immune responses by regulating cytokines, activating immune cells, and reducing inflammation. Key herbs such as Ashwagandha, Turmeric, and Echinacea strengthen both innate and adaptive immunity. Essential oils from herbs like clove and thyme further support immune defense by combating oxidative stress. Ayurvedic Rasayana herbs, including *Glycyrrhiza glabra* and *Tinospora cordifolia*, show promise in cancer prevention and immune rejuvenation. Traditional formulations like Chyavanaprash offer dual roles in preventive care and disease management. Backed by scientific research, herbal immunomodulators represent a sustainable, holistic approach to modern healthcare. This review explores their significance in enhancing immune function and managing chronic conditions.

Key words: Immunity, Herbal Immunomodulators, Bioactive Compounds, Cancer Prevention, Rasayana, Traditional Medicine, Immune Enhancement

Introduction

The immune system is a highly coordinated defense mechanism that protects the body against infections, malignancies, and other diseases. A well-functioning immune system is essential for maintaining health, while dysregulation—either overactivity or suppression—can result in

autoimmune diseases, allergies, chronic inflammation, or increased susceptibility to infections. Immunomodulation refers to the regulation and enhancement of immune responses to maintain an optimal balance between defense against pathogens and the prevention of harmful overreactions (Alanazi et al., 2023).

A wide variety of bioactive phytochemicals, including flavonoids, polysaccharides, terpenoids, and alkaloids, have been shown to influence both cellular and humoral immunity. These compounds may enhance cytokine secretion, promote lymphocyte proliferation, regulate macrophage activity, and modulate immune checkpoints, contributing to balanced immune homeostasis (Kadiyska et al., 2023).

Global health is increasingly challenged by emerging infectious diseases and evolving pathogens, raising concerns about potential pandemics. Furthermore, widespread antibiotic and antiviral resistance have intensified the difficulty of controlling infections. This has fueled interest in alternative therapeutic strategies. Herbal medicines, which have been used for centuries in traditional systems such as Ayurveda, Traditional Chinese Medicine, and Kampo, are now being re-evaluated for their immunomodulatory potential in modern healthcare. Their natural bioactive molecules exhibit antimicrobial, anti-inflammatory, antioxidant, and immune-regulating effects, making them promising candidates for both preventive and therapeutic applications (Kadiyska et al., 2023).

Beyond infection control, immunomodulators are of particular relevance in cancer therapy. Tumour progression is strongly associated with immune evasion strategies, including suppression of antigen presentation, induction of immunosuppressive cells, and manipulation of immune checkpoint pathways. Recent evidence suggests that herbal immunomodulators such as curcumin, andrographolide, and polysaccharides from *Astragalus* and *Tinospora* can counteract these mechanisms by enhancing natural killer (NK) cell activity, regulating cytokine signalling, and improving T cell responses. This dual ability to strengthen immunity and modulate tumour-associated pathways highlights their potential role as adjuncts in cancer prevention and therapy (Alanazi et al., 2023).

Despite several existing reviews, most have either emphasized general immune enhancement or anticancer effects in isolation. There remains a lack of integrative reviews that specifically address the dual role of herbal immunomodulators in immunity enhancement and cancer

control. This review therefore aims to bridge that gap by synthesizing recent advances, critically evaluating mechanistic insights, and identifying future directions for research and clinical translation.

Bioactive Phytochemicals in Immunomodulation

Plants possess a wide variety of secondary metabolites that contribute to their medicinal value. Among these, flavonoids, terpenoids, alkaloids, polysaccharides, and saponins are the most extensively studied for their immunomodulatory effects. These bioactive molecules interact with immune receptors and signaling pathways to regulate both innate and adaptive immunity (Alanazi et al., 2023).

Flavonoids such as quercetin, apigenin, and kaempferol modulate signaling cascades like NF- κ B, MAPKs, and JAK/STAT, thereby reducing proinflammatory cytokines while promoting antioxidant defense. They also protect immune cells from oxidative stress, which is crucial in maintaining effective immune responses. Terpenoids, including andrographolide and withanolides, directly influence lymphocyte proliferation and NK cell activity, enhancing pathogen clearance. Alkaloids such as berberine and vincristine demonstrate immunomodulation alongside anticancer effects, partly by regulating apoptosis and cell cycle checkpoints (Liu et al., 2025).

Polysaccharides from *Astragalus membranaceus* and *Lentinula edodes* (shiitake mushroom) are notable for activating macrophages, dendritic cells, and complement pathways, which bridge innate and adaptive immunity. Saponins, such as those derived from *Panax ginseng*, serve as vaccine adjuvants, enhancing antigen presentation and antibody production. The structural diversity of these phytochemicals underlies their wide range of immunological actions, making them valuable candidates for both prophylactic and therapeutic interventions (Wong et al., 1994).

Herbal Immunomodulators for Immunity Enhancement

Herbal medicines have been used for centuries to strengthen host defense mechanisms and maintain immune homeostasis. Advances in phytochemistry and immunopharmacology have

provided scientific validation for many traditional claims, revealing that herbal immunomodulators act by regulating cytokine production, enhancing immune cell proliferation, and improving innate and adaptive immune responses. Several key herbs have emerged as prominent immunity enhancers (Kadiyska et al., 2023)

- ***Withania somnifera* (Ashwagandha):**

Widely recognized in Ayurveda as a Rasayana herb, Ashwagandha enhances both cellular and humoral immunity. Its bioactive withanolides promote T-lymphocyte proliferation, natural killer (NK) cell activity, and antibody production. Clinical studies indicate its effectiveness in reducing stress-induced immunosuppression and improving immune resilience during viral infections, including COVID-19 (Arun et al., 2024)

- ***Andrographis paniculata* (Kalmegh):**

Andrographis, commonly known as the King of Bitters, belongs to the Acanthaceae family and is extensively used in Ayurveda and Traditional Chinese Medicine (TCM). Its major bioactive diterpenoid lactone, andrographolide, exhibits potent immunomodulatory, antimicrobial, and anti-inflammatory properties. Andrographolide enhances antibody production, activates macrophages, and modulates immune cell responses by inhibiting proinflammatory mediators. These effects contribute to its effectiveness against respiratory infections and inflammatory disorders, while its antioxidant and cytotoxic properties further support its therapeutic potential (Kadiyska et al., 2023; Rajanna et al., 2021; Xi et al., 2022)

- ***Astragalus membranaceus* (Astragalus):**

A cornerstone herb in TCM, Astragalus exerts its immunomodulatory effects primarily through Astragalus polysaccharides (APS). APS activate macrophages, B cells, and Toll-like receptor 4 (TLR4), leading to increased production of cytokines such as IL-1, IL-6, IL-2, and TNF- α . Preclinical studies demonstrate enhanced phagocytosis, regulation of immune responses, and antiviral activity. Astragalus also shows promise in chronic inflammatory conditions such as asthma and diabetic nephropathy (Kadiyska et al., 2023; Wang XY et al., 2022; National Center for Complementary and Integrative Health. 2024)

- **Echinacea purpurea:**

Echinacea is one of the most widely used herbal immune boosters, particularly for the prevention and management of upper respiratory tract infections. Extracts rich in polysaccharides and alkamides stimulate macrophage activation, phagocytosis, NK cell activity, and dendritic cell maturation. By enhancing non-specific immune defenses and cytokine production, Echinacea contributes to strengthened immune responses, although formulation variability influences clinical outcomes (Kadiyska et al., 2023; Zhai et al., 2007).

- **Nigella sativa (Black cumin):**

Nigella sativa has a long history of medicinal use, with thymoquinone (TQ) identified as its principal bioactive compound. TQ modulates Th1/Th2 cytokine balance, enhances splenocyte proliferation, and stimulates NK cell cytotoxic activity. These immunoregulatory effects, along with its antioxidant and radioprotective properties, make black cumin a promising agent for immune support in infectious diseases, autoimmune disorders, and cancer-related conditions (Kadiyska et al., 2023; Ciesielska-Figlon et al., 2023).

- **Elettaria cardamomum (Cardamom):**

Traditionally valued for its digestive and antimicrobial effects, cardamom has recently gained attention for its immunomodulatory properties. Studies indicate that cardamom enhances splenocyte proliferation, alters Th1/Th2 cytokine release, and increases NK cell cytotoxicity. Additionally, modulation of COX-2 and inducible nitric oxide synthase (iNOS) suggests a role in immune regulation and inflammation control. Collectively, these herbs demonstrate the capacity of natural products to enhance both innate and adaptive immunity through multi-targeted mechanisms. However, further well-designed clinical studies are required to establish standardized dosing, long-term safety, and reproducibility of therapeutic outcomes (Abdullah et al., 2023; Kadiyska et al., 2023).

Herbal Immunomodulators in Cancer Control

Beyond infection resistance, immunomodulators play a pivotal role in cancer prevention and therapy by restoring tumor immunosurveillance, regulating inflammatory pathways, and

modulating tumor-associated immune cells. Several herbal agents have shown strong immuno-oncological potential (Kadiyska et al., 2023).

- **Curcuma longa (Turmeric):**

Turmeric, derived from the rhizome of *Curcuma longa*, has been used medicinally for over 5,000 years. Its active compound, curcumin, exhibits potent antioxidant and anti-inflammatory activities by inhibiting NF- κ B activation and reducing proinflammatory cytokines such as TNF- α , IL-1 β , IL-6, and IL-8. Curcumin modulates key signaling pathways, including mTOR and MAPKs, regulating cell proliferation, apoptosis, and survival. Although curcumin has low intrinsic bioavailability, co-administration with piperine significantly enhances its absorption and anticancer efficacy (Kadiyska et al., 2023; Shoba et al., 1998).

- **Glycyrrhiza glabra (Liquorice):**

Liquorice contains glycyrrhizin, glabridin, and isoliquiritigenin, which exhibit immunomodulatory and anticancer activities. These compounds promote T-cell proliferation, inhibit angiogenesis, and induce apoptosis in tumor cells. Liquorice polysaccharides further enhance immune responses, while its hepatoprotective properties support its use as an adjuvant in chemotherapy (Kadiyska et al., 2023; Bisht et al., 2022).

- **Zingiber officinale (Ginger):**

Ginger rhizomes are rich in gingerols, shogaols, phenolic compounds, and polysaccharides. These bioactives suppress inflammatory mediators such as TNF- α and IL-1 β , inhibit prostaglandin biosynthesis and arachidonate 5-lipoxygenase, and induce apoptosis in cancer cells. Ginger also contributes to wound healing and exhibits chemopreventive potential by modulating multiple molecular pathways (Kadiyska et al., 2023).

- **Lentinula edodes (Shiitake mushroom):**

Shiitake is a medicinal mushroom known for its antitumor and immunomodulatory properties. Its β -glucan polysaccharide, lentinan, binds to pattern recognition receptors such as dectin-1 on macrophages, dendritic cells, and neutrophils. This interaction activates immune signaling pathways, enhancing the production of cytokines like TNF- α , IL-12, and IFN- γ , thereby improving NK cell activity and chemotherapy tolerance (Kadiyska et al., 2023; ai et al., 2015).

- **Tinospora cordifolia (Guduchi):**

Widely used in Ayurveda as an immune-rejuvenating Rasayana herb, Guduchi enhances macrophage function, stimulates cytokine production, and exhibits cytotoxic activity against tumor cells. It is also known to reduce chemotherapy-induced toxicity and improve overall immune resilience (D Shedbale et al. 2025)

Together, these herbal immunomodulators target multiple hallmarks of cancer, including chronic inflammation, immune evasion, angiogenesis, and tumor cell survival. Their multitargeted actions offer synergistic benefits when combined with conventional cancer therapies. However, successful integration into clinical oncology requires standardized extracts, mechanistic clarity, and robust clinical trials to ensure safety and efficacy (Kadiyska et al. 2023; Alanazi et al. 2023)

Herb	Active Compounds	Immunological Actions	Therapeutic Effects
Andrographis (<i>Andrographis paniculata</i>)	Andrographolide (diterpenoid lactones)	Enhances antibody production, modulates immune cells, anti-inflammatory	Antioxidant, antimicrobial, cytotoxic, and hepatoprotective
Astragalus (<i>Astragalus membranaceus</i>)	Astragalus polysaccharides (APS)	Activates macrophages and B-cells; enhances cytokine production	Antitumor, antiviral, antibacterial; useful in asthma and nephropathy
Black Cumin (<i>Nigella sativa</i>)	Thymoquinone (TQ)	Modulates Th1/Th2 balance; enhances NK cell activity	Radioprotective, antioxidant; useful in autoimmune diseases and cancer
Cardamom (<i>Elettaria cardamomum</i>)	1,8-Cineole and other volatile oils	Alters Th1/Th2 cytokines; enhances NK cell cytotoxicity	Anticancer potential, antimicrobial, digestive aid

Echinacea (<i>Echinacea purpurea</i>)	Polysaccharides, alkamides	Stimulates macrophages and NK cells; enhances cytokine release	Common cold prevention; promotes dendritic cell maturation
Ginger (<i>Zingiber officinale</i>)	Gingerol, shogaol, zingibain	Suppresses TNF- α and IL-1 β ; inhibits prostaglandin synthesis	Anti-inflammatory, wound healing, cancer prevention
Liquorice (<i>Glycyrrhiza glabra</i>)	Glycyrrhizin, glabridin, polysaccharides	Promotes T-cell proliferation; inhibits tumor growth	Chemotherapy adjuvant, anti-inflammatory, hepatoprotective
Shiitake (<i>Lentinula edodes</i>)	Lentinan (polysaccharide)	Activates immune receptors (e.g., dectin-1); increases TNF- α and IFN- γ	Antitumor, hepatoprotective, enhances bone marrow response
Turmeric (<i>Curcuma longa</i>)	Curcumin	Inhibits NF- κ B; reduces TNF- α and IL-6; modulates immune signaling	Antioxidant, anti-inflammatory; bioavailability enhanced with piperine

Table 1: common herbal immunomodulators with their active compounds, immunological actions, and therapeutic applications

Immunomodulatory Properties of Herbal Medicines and Their Essential Oils

A wide range of herbs—including *Laurus nobilis* (bay laurel), *Nigella sativa* (black cumin), *Syzygium aromaticum* (clove), *Foeniculum vulgare* (fennel), *Melissa officinalis* (lemon balm), *Cymbopogon citratus* (lemongrass), *Origanum majorana* (marjoram), *Mentha piperita* (peppermint), *Rosmarinus officinalis* (rosemary), *Salvia officinalis* (sage), and *Thymus vulgaris* (thyme)—are traditionally incorporated into diets and medicinal preparations due to their immunomodulatory potential. Recent pharmacological studies confirm that their essential

oils exert multiple beneficial actions, including suppression of pro-inflammatory mediators, enhancement of antioxidant defenses, and activation of immune cells (Pelvan et al., 2023; Kadiyska et al., 2023)

Essential oils are typically rich in monoterpenes (e.g., 1,8-cineole, thymol, carvacrol), sesquiterpenes, and phenolic compounds, which regulate cytokine networks and modulate oxidative stress. For instance, thyme and rosemary oils have been shown to decrease TNF- α and IL-6, while promoting IL-10 release. Similarly, black cumin oil (thymoquinone) has been found to enhance NK cell cytotoxicity, thereby improving host defense against infections and tumors. While promising, variability in extraction methods and dose standardization remain barriers to consistent clinical application (Arun et al., 2024; Zhou et al., 2022).

Herbal Immunomodulators and Cancer Prevention

Cancer is a complex disease characterized by the transformation of normal cells into malignant tumors, often involving immune system dysregulation. Rasayana herbs, an essential part of Ayurveda, have demonstrated significant anticancer activity by reducing oxidative stress, detoxifying cells, and enhancing immune function. *Glycyrrhiza glabra* (liquorice) exhibits cytotoxicity against colon and breast cancer cell lines⁴, while *Asparagus racemosus* has shown efficacy against non-small cell lung cancer in preclinical studies⁵. Other herbs, such as *Tinospora cordifolia*, *Aegle marmelos*, and *Bacopa monnieri*, also display anticancer potential by modulating cytokine profiles and improving antioxidant status. Importantly, many of these effects are immunologically mediated rather than purely cytotoxic, suggesting that Rasayana herbs may serve as safe, long-term preventive agents. However, robust clinical evidence is lacking, as most studies remain at in-vitro or animal stages (Patekar et al., 2022).

Herbal Formulations in Immunomodulation and Cancer Adjuvant Therapy

Ayurvedic formulations such as Chyavanaprash, Amalaki Rasayana, and Gokshura Rasayana incorporate multiple immunomodulatory herbs in synergistic combinations. These formulations not only strengthen immunity but also act as adjuvants during cancer treatment by reducing treatment-related toxicities and improving quality of life. Clinical observations suggest improved immune resilience among populations regularly consuming Chyavanaprash, though more controlled trials are warranted. Daily dietary incorporation of immunomodulatory

herbs like *Boerhavia diffusa* (Punarnava), *Tinospora cordifolia* (Guduchi), *Bacopa monnieri* (Brahmi), *Embllica officinalis* (Amalaki), *Leptadenia reticulata* (Jivanti), and *Curcuma longa* (Turmeric) has been linked to long-term improvements in immunity and reduced incidence of chronic disease (Patekar et al., 2022).

Nutritional and Preventive Role of Herbal Immunomodulators

In addition to direct immunostimulatory activity, herbal immunomodulators address nutritional deficiencies that impair immunity. Compounds such as polyphenols, terpenoids, and β -glucans act as antioxidants, free-radical scavengers, and anti-inflammatory agents. By improving nutritional status, they not only enhance immune function but also reduce the risk of lifestyle-related diseases such as metabolic syndrome, diabetes, and cancer. Preventive roles are particularly important in populations with high genetic predisposition to chronic diseases (Behl et al., 2021).

Role of Rasayana Herbs in Immunomodulation

Rasayana therapy in Ayurveda is designed to rejuvenate tissues (Dhatus), strengthen vitality (Ojas), and maintain bio-strength (Bala). Modern research confirms these herbs stimulate spleen cell proliferation, enhance bone marrow cellularity, and improve macrophage and NK cell activity. For instance, *Tinospora cordifolia* and *Withania somnifera* have demonstrated immunostimulant activity in both experimental and clinical studies. *Aegle marmelos* improves T-cell responses, while *Bacopa monnieri* enhances cognitive and immune health, highlighting their dual therapeutic value (Patekar et al., 2022; Sawane et al., 2019).

Herbal Immunomodulators in Strengthening Immunity: Community Evidence

Recent field-based surveys in Kerala explored herbal immunomodulator use for general immunity strengthening. Commonly consumed herbs included Tulsi (*Ocimum sanctum*), Turmeric (*Curcuma longa*), Moringa (*Moringa oleifera*), and Amla (*Embllica officinalis*). Tulsi emerged as the most widely used, often consumed as tea or decoction. The survey revealed a preference for single-herb remedies, minimal side effects, and concurrent use with allopathic medications. Additionally, Ayurvedic formulations like Chyavanaprash and Ashwagandha powder were widely adopted. These findings emphasize the growing public reliance on herbal remedies for preventive healthcare and lifestyle disease management (Marva et al., 2024).

Conclusion and Future Perspectives

Herbal immunomodulators and their essential oils are increasingly recognized as promising agents in maintaining immune homeostasis and combating complex diseases such as cancer. They strengthen the body's defenses by regulating cytokine production, modulating cellular and humoral immunity, and providing antioxidant protection. Herbs such as *Tinospora cordifolia*, *Glycyrrhiza glabra*, *Curcuma longa*, *Ocimum sanctum*, and *Withania somnifera* have demonstrated significant immunomodulatory, anti-inflammatory, and anticancer activities, supporting their use in both traditional medicine and modern therapeutics.

The present review highlights that, while there is considerable experimental and clinical evidence supporting the role of herbal immunomodulators, several limitations remain. These include variability in phytochemical content due to differences in cultivation and harvesting, lack of standardized formulations, poor bioavailability of active constituents, and limited well-designed clinical trials. In addition, herb–drug interactions and underreported adverse effects necessitate careful evaluation and pharmacovigilance.

Moving forward, future research must address these challenges. Integration of advanced analytical tools such as metabolomics, proteomics, and systems biology will help unravel the molecular mechanisms underlying immunomodulation. Development of standardized extracts and novel delivery systems, such as nanoparticles and liposomes, may improve bioavailability and therapeutic efficacy. Moreover, multi-centered, randomized clinical trials are urgently required to validate safety, efficacy, and dosage guidelines in diverse populations.

Beyond preventive health, herbal immunomodulators hold immense promise as adjuvants in cancer therapy, particularly in enhancing the efficacy of immunotherapies and reducing treatment-related side effects. Traditional Ayurvedic formulations such as Chyavanaprash and Amalaki Rasayana, when validated through modern research, could serve as integrative tools in holistic healthcare.

In conclusion, herbal immunomodulators serve as a bridge between traditional wisdom and modern biomedical science. Their ability to enhance immunity, reduce inflammation, and prevent chronic diseases underscores their value in global healthcare. With rigorous research,

standardization, and clinical validation, these natural agents may become indispensable in the prevention and management of immune-related disorders and cancer, ultimately improving health outcomes and quality of life.

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