



**INTERNATIONAL JOURNAL OF
PHARMACEUTICAL SCIENCES**
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: <https://www.ijpsjournal.com>



Review Paper

Immune System Modulation with Traditional Herbs

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ARTICLE INFO

Published: 22 Jan 2026

Keywords:

Plant-derived immunomodulators, bioactive plant constituents, Immune system, Ayurveda structure, Immunostimulant, Immunosuppression, human studies.

DOI:

10.5281/zenodo.18338671

ABSTRACT

Immunomodulators have the ability to either enhance or downregulate immune responses against pathogens, malignancies, and injury. In recent years, significant scientific interest has focused on natural and plant-based immunomodulators due to their long-standing use in traditional medicine systems and their comparatively fewer side effects. This comprehensive review examines the concept of immune modulation and critically evaluates key medicinal herbs known to influence immunity, including *Withania somnifera*, *Tinospora cordifolia*, *Curcuma longa*, and *Ocimum sanctum*. The roles of bioactive plant constituents such as alkaloids, flavonoids, terpenoids, and polysaccharides in modulating immune cells, cytokine production, and signaling pathways (e.g., NF- κ B and MAPK) are discussed. Evidence from human studies, including Ayurvedic regimens for SARS-CoV-2 infection and Ashwagandha clinical trials, is reviewed along with safety, standardization challenges, and future research directions. Overall, plant-derived immunomodulators show promise, although robust clinical evidence and quality control are essential for their integration into modern healthcare.

INTRODUCTION

The immune system plays a central role in protecting the body from infections, abnormal cell growth and inflammatory disorders [1]. Immunomodulators are substances that help restore balance by either boosting weak immunity or calming excessive activity. The immune system

has two main components. The innate immune response acts quickly and provides general protection through physical barriers, phagocytic cells, and inflammatory mediators [14]. The adaptive immune response is slower but highly specific, using B - and T-lymphocytes to build targeted defense and long-term memory [19]. Interest in plant-based immunomodulators has

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



increased because many medicinal herbs used in Ayurveda and other traditional systems [18] contain compounds that influence immune pathways with fewer side effects than synthetic agents [4]. Many herbs possess antioxidant, anti-inflammatory, or immune-supportive properties [27]. This review highlights how selected herbs modulate immune activity, the bioactive constituents involved, and available experimental and clinical evidence supporting their use. Controlling immune responses is important in terms of diseases caused by infection, cancer, autoimmunity, or inflammation. Immunomodulators refer to the agents that either enhance or decrease the activities of the immunity to bring about equilibrium. The body's immune defense is two layered; Non-specific innate immunity is quick and does not have any adaptive immunity and adaptive immunity has a slower response with specific lymphocytes. Efficient immunomodulators have the potential to improve low responsiveness (i.e. in case of infection or cancer treatment) or suppress excessive activity in immunity (i.e. in autoimmunity). Researchers are turning more attention toward plant-derived immunomodulators, as many of them appear to plants have traditionally been used in Ayurveda systems and other traditional systems, and current studies imply that they can positively affect immunity with fewer side effects than the synthetic medications do. For example,

inflammation-modulating and antioxidant activities have been shown by natural compounds derived from medicinal plants. This review will critically analyze the nature of immunomodulation, immune pathway, list of potential immunomodulators identified active fraction of the plant), studies conducted in humans have examined efficacy, safety, and future perspective of plant-derived immunomodulators.

MECHANISMS AND IMMUNOMODULATION

immunostimulation vs immunosuppression

Immunomodulators are able to stimulate immune response (immunostimulants), or suppress (immunosuppressants) [7]. Immunostimulants serve to stimulate innate defense (phagocytes, NK cells) [30] and adaptive reaction to aid in overcoming infection and cancer. Conversely, immunosuppressants suppress immune response to manage autoimmune responses or transplant rejection [25]. The related category is immunoadjuvants (now is an anti-vaccination word), a substance (typically administered together with vaccines) that amplifies the antigen-specific immune response [26]. As an illustration, herbal extract may be used as a natural vaccine adjuvant by enhancing antibody responses and T- cells activation.

Table No.1 Selected Ayurvedic Herbs and Their Immunomodulatory Actions

Plant Name (Ayurvedic Name)	Bioactive Constituents	Immunomodulatory Action	Mechanism of Action	Type of Study	Key Findings
Withania somnifera (Ashwagandha)	Withanolides	Immunostimulant	Enhances NK cell activity, increase cytokine production	Clinical trial	Improved immune response and stress tolerance

Tinospora cordifolia (Guduchi)	Alkaloids, glycosides, polysaccharides	Immunostimulant	Activates macrophages and humoral immunity	Human study	Increased antibody production
Curcuma longa (Turmeric)	Curcumin	Immunosuppressant / Immunomodulator	Inhibits NF-kB, regulates cytokines	Clinical studies	Reduced inflammation and immune overactivity
Ocimum sanctum (Tulsi)	Eugenol, flavonoids	Immunostimulant	Modulates T-cell and B-cell responses	Human trial	Enhanced immune markers

principles of immune

Consisting of fundamental defense elements, with the skin as a leading component, the innate immune system provides immediate defense, mucosa), phagocytic cells (macrophages, neutrophils, dendritic cells), and NK along with recognizing the pathogen through pattern-recognition receptors (TLRs, NLRs) [18] and causing inflammation. The adaptive immune network - largely dependent on B and T lymphocytes - enables specific pathogen recognition gives pathogen specific immunity and immunological memory. These responses are mediated by cytokines (e.g. IL-2, IFN-g, TNF-a) [16] and antibody. Immunomodulators produced by plants have the capability of affecting both arms. For example, the bioactive plant constituents can stimulate the macrophages [28] and dendritic cells, which secrete cytokines that regulate immunity. Conversely, they can inhibit hyperactive pathways by inhibiting such factors as NF-kB to decrease cytokines [34].

HERBAL MEDICINE THAT HAS IMMUNOMODULATOR ACTIVITY

Withania somnifera (Ashwagandha) Ashwagandha is a well-known rejuvenating herb in Ayurveda. Its roots contain withanolides, alkaloids, and saponins, which are linked to its

biological activity. Studies show that Ashwagandha can support the immune response by improving the activity of T-lymphocytes, natural killer (NK) cells, and macrophages. Tinospora cordifolia (Guduchi) Guduchi is valued in traditional medicine for its ability to modulate inflammation and immune responses. Its stem contains diterpenoids, alkaloids, and glycosides that influence cytokine production and cellular signaling. Curcuma longa (Turmeric) Turmeric contains curcumin and other curcuminoids widely studied for anti-inflammatory and antioxidant effects. Ocimum sanctum (Tulsi) Tulsi contains eugenol, ursolic acid, and flavonoids that support immune balance and reduce inflammation. The body's immune defense has been described as modulated by many plants. In the following, some important herbs will be listed, which have either experimental or clinical evidence: Withania somnifera (Ashwagandha) – Ashwagandha is an Ayurvedic rasayana, and its roots have withanolides, alkaloids, and saponins [15]. It has an extract that has inflammation-modulating and antioxidant effects. Research indicates that Ashwagandha maintains homeostasis in adaptive immunity. It enhances the growth of T-cells, cytokines (i.e. IL-2, IFN-g), and macrophages. For example, a single trial established that Ashwagandha supplementation increased the pour of T- cell-4+ and CD56+ deactivated NK



cells in healthy adults [20, 21]. This is because its traditional application in stress resistance and infection resistance can be linked to these immune boosts. P65 and prevented the expression of IL-6 and TNF- α of *Tinospora cordifolia* (Guduchi) – *Tinospora* is an Ayurvedic a plant known to influence immune and inflammatory pathways, with stems containing high levels of alkaloids, glycosides, diterpenoids (of the clerodane types), and steroids [3]. Experimental literature suggests that it possesses strong inflammation-modulating properties and that it has the effect of promoting an optimal immune response. The pharmacological studies indicate that *T. cordifolia* extracts regulate the pathways of cell growth and cytokine synthesis. Indicatively, a study on animals discovered that *T. cordifolia* suppressed inflammatory cytokines (TNF- α , IL-1b) and iron homeostasis in an infection model. *Tinospora* has been widely used clinically as herbal formulations to boost immunity in the face of infection; a recent SARS-CoV-2 infection study found that a combination of Giloy (*tinospora*), Ashwagandha and Tulsi hastened the removal of viruses and reduced IL-6 and TNF- α significantly [11,25]. *Curcuma longa* (Turmeric) – Curcumin, desmethoxycurcumin and various curcuminoids are polyphenols found in turmeric and are inflammation-modulating agents. Curcumin suppresses NF- κ B, JAK/STAT and other pro-inflammatory pathways. In cell cultures, *C. longa* extracts inhibited the activity of NF- κ B inflamed endothelial cells. Polysaccharides in turmeric have the potential to activate immune cells as well; one review found that *C. longa* fractions stimulated the production of IL-10, IL-5 and GM-CSF, suggesting that B-cells and macrophages were activated. Animal study indicates that turmeric extract will reduce pro-inflammatory cytokines (IL-1b, IL-6, TNF- α) and enhances immune cell maintenance in diabetic rats. Hence, turmeric regulates the

activities of inflammatory mediators (immunosuppressive effect) and innate effectors. Bio actives (e.g., curdione and turmerones), compounds demonstrating immune-modulating properties, are present in other *Curcuma* species (e.g., *C. zanthorrhiza*, *C. zedoaries*). *Ocimum sanctum* (Holy Basil or Tulsi) – Tulsi is regarded as a sacred Ayurvedic plant, the foliage and seeds act as prominent natural sources of eugenol, ursolic acid, flavonoids as well as polyphenols. Experimental data support that these compounds are immunomodulatory [8]. Citing an example, Tulsi seed oil (*Ocimum sanctum* seed oil) had boosted antibody titer and maintained humoral and cell-mediated immunity during stress. It also suppressed allergic release of histamine connoting that it has inflammation-modulating effects. The bioactive plant constituents (eugenol, ursolic acid) present in tulsi have been said to boost the total immune system. Overall, Tulsi seems to increase NK-cell performance and antibody response and suppress inflammatory mediators [12,29,33]. Other distinguished herbs: *Echinacea purpurea* has alkamides and polysaccharides which induce phagocytosis and cytokine secretion [17]. Bioactive plant constituents that include antiviral and immunostimulatory effects are lignan and flavonoid in *phyanthus niruri* [23]. Noni polysaccharides of *Morinda citrifolia* are activators of the macrophage and T-cells. Thymoquinone is found in *Nigella sativa* (black seed), and studies involving this gene have been able to regulate Th1/Th2 and anti-inflammatory effects [5,22]. *Astragalus* membrane polysaccharides have been known to stimulate the macrophage activity and dendritic cell activity [9]. These cases represent a wide range of plant immunomodulators in the recent literature. The action of every herb is dependent on its active chemicals. Summing up the findings, these medicinal plants exhibit a variety of



immunoactivity compounds (flavonoids, terpenoids, alkaloids, polysaccharides) that may stimulate or suppress the body's immune defense (antibodies, T-cells, macrophages and NK cells) or suppress overexpressed inflammation [2].

MECHANISMS OF ACTIONS OF PLANT DERIVED PRODUCTS

Plant-derived immunomodulators work through several mechanisms:

1. Regulation of cytokines
2. Activation of innate immune cells
3. Antioxidant protection
4. Influence on signaling pathways
5. Adaptive immunity modulation

The action of plant-derived immunomodulators has many mechanisms:

cytokine regulation

The cytokine profiles are changed by a lot of bioactive plant constituents. For example, they can antagonize NF- κ B- and MAPK-pathways (critical mediators of pro-inflammatory [13]. Cytokines such as TNF- α , IL-6). Curcumin is the well-known inhibitor of NF- κ B with decreased production of TNF- α and IL-6. At the same time, there are herbs, which stimulate inflammation-modulating cytokines (e.g. IL-10) to stabilize the body's immune defense [24]. Consequently, Herbs will be able to suppress chronic inflammation and permit proper clearance of pathogens.

macrophage and innate cell activation

There are a lot of plant compounds that directly stimulate the innate immune cells. For example, polysaccharide extracts of Echinacea and Morinda stimulate receptors on macrophages and dendritic cells eliciting cytokine activity, including that of IL-1 β , IL-12), as well as

phagocytosis. Macrophages activation increases T-cells antigen presentation. Plant flavonoids and saponins such as those of Tinospora and Asparagus also have the ability to stimulate macrophage no and microbicidal activity [6].

antioxidant effects

A great number of immunomodulatory herbs contain antioxidants (polyphenols, Vitamins). They eliminate oxidative stress caused by free radicals, which raises inflammation levels otherwise. To mention something, ashwagandha and turmeric possess a great antioxidant ability that helps to preserve immune cells. This antioxidant action is indirectly beneficial in a healthy immune functioning. Signaling Pathways bioactive plant constituents act on particular signaling molecules. For example, Curcuma compounds regulate JAK-STAT and MAPK signaling of lymphocytes, which influences cell proliferation and differentiation. Tinospora alkaloids can prevent pro-inflammatory enzyme and capabilities. Overall, the effects of plant-derived immunomodulators are to suppress chronic inflammation by modifying major immune pathways (NF- κ B, MAPK, JAK/STAT) or enhance the Protection responses by macrophages.

pattern recognition and adaptive effects

According to some botanicals, pattern recognition receptors on immune cells (TLRs) are more sensitive to the effect of the innate immunity. Others modulate adaptive immune response i.e. favor production of Th1-type responses (IL-2, IFN- γ) as opposed to Th2. On the example of Tulsi and Echinacea, the Th1/Th2 ratio is shifted towards the Th1, which helps in viral immunity and cancer immunity. Overall, plant-derived immunomodulators have a pleiotropic effect. Flavonoids, terpenes, alkaloids and



polysaccharides interrelate to restore immune homeostasis – by activating some cells, and fix excessive inflammation. One common aspect is that such bioactive plant constituents have the effect of activating macrophages, inducing/stimulating the synthesis of cytokines, and modulating fundamental signal transduction to reinstate immune homeostasis.

HUMAN STUDIES, EVIDENCE AND HUMAN TRIALS

Although human research is limited, several investigations show the immunomodulatory potential of herbs such as Ashwagandha, Tinospora, and Tulsi. These studies report improvements in immune cell activity, reduced inflammation, and better recovery in mild infections [10]. There are some human investigations in herbal immunomodulatory advantage, albeit trials are rigorously few. Key findings include: Ashwagandha studies: In a small human study, Ashwagandha extract (used with anupana) caused a significant increment in the number of CD4+ T-cells and also the activation of the CD56 + NK cells in 96 hours. A different RCT of stressed individuals found that Ashwagandha supplementation lowered cortisol and stress scores suggesting the enhancement of immune functioning via neuroendocrine adaptation. The evidence indicates that Ashwagandha can enhance cellular immunity related indicators and stress induced immune dysfunction. Ayurvedic regimen against SARS-CoV-2 infection Ayurvedic regimen In an RCT of asymptomatic SARS-CoV-2 patients, a 7-day Ayurvedic regimen (Tinospora cordifolia, Ashwagandha, Ocimum sanctum, and other rasayanas) accelerated the process of viral clearance relative to placebo. On day 7, 100% of the treated patients were virus-negative (compared to 60% controls) [35]. Notably, hs-

CRP, IL-6 and TNF- α increased by 12.4, 2.5 and 20 times, respectively in treated patients compared to controls.

There were no side effects. This pilot study suggests that herbal regimen has the potential of increasing natural immunity and decreasing the inflammation in human beings. Tinospora in immune challenge: Early human evidence points to the possibility of Tinospora reducing the symptoms of chronic infections [11]. For example, one of the older trials indicated that Tinospora extract had immunostimulant effect in HIV patients (enhanced CD4 counts) but there is limited data.

echinacea research

Meta-analysis of Echinacea RCTs in the upper respiratory decreases below the double that of cold duration and severity, suggesting that it is an immunostimulant. The outcome however is different in different species and preparation thus the need to have standardized products.

other herbs

Clinical action of turmeric as an immunomodulatory may be indirect (e.g. suppression of markers of inflammatory diseases such as arthritis and metabolic syndrome). There were positive reports of increased antioxidant status of smokers and asthma patients on some trials of Tulsi extracts, indicating immune support. Overall, human trials give evidence of proof-of-concept that plant-derived immunomodulators can positively change immune markers and symptoms, although bigger RCTs are necessary. Findings are positive but tentative. An example of the potential of Ashwagandha is the small-scale trial to improve the activation of T-cells and NK-cells, an example of actual efficacy is the Ayurvedic



SARS-CoV-2 infection study, which has shown an increase in antiviral immunity [29,31].

SAFETY, TOXICITY AND STANDARDIZATION ISSUES

Plant-derived immunomodulators are widely considered safe, however, caution should be taken. Most of them have broad therapeutic indices and can be safely utilized over long durations with minimal toxicity. For example, Ayurvedic regimen against SARS-CoV-2 infection was conducted with no adverse effects. Plant immunomodulators have fewer side effects compared to synthetic immunosuppressants. However, there are toxicity issues. Other herbs have a potential interaction with drugs or are contraindicated in autoimmune disorders in scenarios where dosing surpasses the therapeutic range.

the problem of quality issues is a significant one

Cases of contamination with heavy metals (lead, mercury, arsenic, cadmium) have been detected in some lots of herb products. It is imperative to ensure that heavy metals do not exceed safe levels by methods such as the ICP-MS to test levels [7]. Pesticides and adulteration may also take place and this needs strict testing. Standardization is very important but difficult. Active content of compounds differs depending on the plant source, conditions of growth as well as method of extraction. Having no standardization, batches of different batches of Ashwagandha or Giloy can contain vastly dissimilar levels of withanolides or alkaloid [26]. The variation of this causes uneven efficacy. Such modern quality control techniques as fingerprint chromatography and measurements of the compounds of the markers are suggested [32]. As an illustration, supplements of turmeric ought to assure a content of curcuminoids whilst

the extracts of Ashwagandha ought to normalize total withanolides content. Regulations of the use of plant-derived immunomodulators are not as suitable as the pharmaceuticals. Thus, the practitioner should be cautious to use such products or crafted by established producers maintaining consistent quality benchmarks manufacturers practice (GMP). In summary, the clinical application of such herbs can be safe (and even helpful); however, purity, dosages, and possible interactions need to be considered.

RECENT TRENDS AND FUTURE PROSPECTS

Increasing global interest in the use of plant-derived immunomodulators has been on the increase. The SARS-CoV-2 infection pandemic has prompted studies on botanicals (e.g. Tinospora, Tulsi, Andrographis) that have the potential to assist with anti-viral immunity. Plant-derived vaccine adjuvants-saponins and polysaccharides are increasingly being investigated as immunostimulators with minimal immunotoxicity and antigen-specific responses. Indicatively, plant polysaccharides are under study to enhance SARS-CoV-2 infection vaccine activity. The trends in technology involve the application of the use of omics and network pharmacology to the concept of multi-target effect of herbs, use of nano formulations to enhance the bioavailability of bioactive plant constituents (e.g. nano-curcumin). Researchers have reported a steady increase in integrative human studies, which subsequently test plant-derived immunomodulators as production factors in chronic illness or immunotherapy of cancer. The next RCT areas involve rigorous standardization of herbal extracts, dose finding, and large scale RCT within clinically characterized patient segments. According to one of the reviews, future research directions should



include, which should be undertaken, has to be the standardization of formulations, which determines optimal dosages as well as proven safety and efficacy in the clinical environment. Consumer trust will be strengthened by the improvement of quality control (DNA barcoding, metabolite, profiling), as well as harmonization of global regulations. Ultimately, bridging the gap between unconventional and modern immunology can achieve new drugs: immunomodulators produced by plants have a huge potential due to their safety and efficacy as immune-supporting agents, yet to achieve this, pharmacological and clinical validation is necessary.

CONCLUSION

Plant-based immunomodulators offer promising support for regulating immune function. Their bioactive compounds influence cytokines, immune cells, and signaling pathways. While early clinical findings are positive, stronger research and better standardization are required for broader acceptance. Plant-derived immunomodulators are a valuable adjunct to the conventional medicine. Conventional herbal products such as Ashwagandha, Giloy, Turmeric, and Tulsi have bioactive plant constituents, which may boost weak immune systems or moderate over inflammation [18]. These compounds have multiple (mechanistically many) targets—macrophages, T-cells, cytokines and signaling pathways (e.g. NF- κ B, MAPK) to re-establish immune homeostasis. Though still in limited human investigations, they have been demonstrated to have positive effects (e.g. increase in NK-cell activity, decrease in proinflammatory factors) and overall excellent tolerability. However, the issues of safety and standardization have to be guided skillfully to bring out the best performance of plant-derived

immunomodulators. Plant-derived immunomodulators have potential to play a significant part with better controlling the quality and with better attestations through human studies with preventive and therapeutic approach related to infections, inflammatory disorders, and possibly even in complementary treatment as in cancer immunotherapy. This critical review highlights that medicinal plants can still be a beneficial source of immunomodulatory agents and thus calls on a need to conduct more detailed studies on how the medicinal plants might be implemented in healthcare in a responsible manner [32].

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HOW TO CITE: Srinivas Thota¹, Anusha Chinnapureddy ², Thanga Balan B³, Immune System Modulation With Traditional Herbs, *Int. J. of Pharm. Sci.*, 2026, Vol 4, Issue 1, 2264-2273. <https://doi.org/10.5281/zenodo.18338671>

