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

Review Paper

Immunomodulatory Medicinal Plants

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ARTICLE INFO

Published: 13 Feb 2026
Keywords:
Medicinal Plants, immune responses, immunodrug
DOI:
10.5281/zenodo.18628909

ABSTRACT

The immune system maintains homeostasis through a highly coordinated network of cellular and molecular interactions regulated by cytokines and their receptors. Disruption of this balance can result in immune-related disorders, prompting the need for effective immunomodulatory therapies. Although synthetic and biological immunodrugs have shown clinical efficacy, their high cost and adverse effects have driven increasing interest toward traditional medicinal systems such as Ayurveda and Siddha, which utilize plant-based formulations for immune enhancement and regulation. Numerous medicinal plants possess potent immunomodulatory activities, influencing both innate and adaptive immune responses through mechanisms that enhance phagocytosis, antibody production, and cytokine expression. In this review, immunomodulatory potential of several medicinal plants—including Withania somnifera, Morus alba, Sophora subprostrata, Acacia catechu, Jatropha curcas, Achillea wilhelmsii, Picrorhiza scrophulariiflora, Plantago asiatica, Panax ginseng, Caesalpinia bonducella, Allium sativum, and Cynodon dactylon—is summarized based on in vitro and in vivo experimental studies. These plants demonstrate diverse mechanisms of immune stimulation and suppression, supporting their traditional use and highlighting their potential as sources for novel immunotherapeutic agents. Continued pharmacological investigation, standardization, and clinical validation of these herbal immunomodulators may lead to the development of safe, affordable, and effective alternatives for immune-related disorders.

INTRODUCTION

Immune homeostasis is maintained by the immune response through the prompt interaction of several cell types in particular microenvironments. In both homeostatic and pathological situations, the variable distribution and regulated expression of cytokines and their receptors offer the selectivity and flexibility required to control cell traffic. Cytokines are therefore reasonable targets for therapeutic immune regulation since they are in charge of the development of phenotypes. Synthetic organics, biological substances like

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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.

cytokines, antibodies, microorganisms, and botanical natural products are examples of immunodrugs. These substances affect immunoregulatory cascades to produce their particular stimulatory, suppressive, or regulatory effects. For clinical purposes, immune suppression has been extensively researched [1]. The Ayurvedic system of medicine, which originated in India, played a significant role in both disease prevention and treatment. There are numerous plants that exhibit immunomodulatory effects. Despite being available, conventional immunomodulatory chemotherapy is more expensive and typically out of reach for average people with modest incomes. Therefore, traditional medicinal plant products' ability to modify the immune system has emerged as a topic for ongoing scientific research around the globe. In the classical texts of Siddha and Ayurveda, a vast array of medicinal plants have been recommended for the treatment of many illnesses that lead to immunological deficiencies. According to the current study, siddha is used as an immunomodulator in the healthcare system in Ayurveda [2]. Both the adaptive and innate immune systems of the organism are affected by these natural or manufactured compounds, or their combinations. Traditionally, therapeutic herbs, including their own natural products and chemical ingredients, have been utilized to modulate the human immune system [3]. These natural products have been used for many illnesses and disorders since ancient times. The immunological response that is currently delivered by their common therapy based on their condition and illness state is known as immunomodulation. Autoimmune diseases are caused by an immunological response that is triggered by a host defense mechanism that generates an immune suppressor. The body's defense system, immunity, neutralizes antigens and keeps the body safe. Immunomodulation is the straightening of suppression that highlights humoral immunity, cellular, non-specific protective constituents, which are pharmaceutical drugs that demonstrate immunomodulatory effects based on dosage. They function as both immunostimulators and immunosuppressors [4].

IMMUNITY AND CLASSIFICTION OF IMMUNOMUDULATORS :

Immunity, which is actually a complicated system with several shields, is the body's primary essential fundamental architecture. The skin serves as the main barrier or shield; in this case, the body's pH and temperature may be too high for the needs at hand. Even though the bacteria enter the body, either the innate or acquired immune systems trigger them [5]. In reaction to foreign and hazardous things, one of the main immune defenses is innate immunity. An immune defense system that is programmed with receptors for prompt response is called innate immunity. In this case, no genetic recombination or other procedure is required [6]. Biological response modifiers, immunomodulators, immunorestoratives, and immunoaugmentors are biomolecules of synthetic or biological origin that have the ability to inhibit, modulate, and stimulate every aspect of the immune system, including the innate and adaptive immune systems [7].

Immunomodulators are typically categorized in clinical practice as immunostimulants, immunoadjuvants, and immunosuppressants :

Immunoadjuvants- Known as immune stimulants, these are used to increase the potency of preparations and injections. It is believed that they are authentic immune system modulators. Their manipulation as selectors among cellular and humoral assistant/helper T1 (TH1) and helper T2 cells (TH2), immune-protective, immune-destructive, and immunoglobulin E vs. immunoglobulin G (IgE vs. IgG) reactions is

frequently observed, which presents a huge challenge for the designers of vaccines and shots [8].

Immunostimulants - It is believed that these will strengthen the body's defenses against infection, which is inherently imprecise. They can respond either innately or adaptively to immunological stimuli. Since they raise the body's basic immunological level, these are known as immunopotentiators and promoters [9].

Immunosuppressants- In addition to being administered in combination to treat various types of tissue/organ transplant rejection and autoimmune disorders, they are regarded as an inherently and operationally diverse family of medications [10].

METHODS FOR TESTING IMMUNOLOGICAL FACTORS:

The standard screening procedure involves taking a single constituent or distilled fraction from herbal medications and using traditional pharmacological methods to assess its bioactivity. Since it appears to be able to react to the effectiveness, side effects, and toxicity of medications as a whole, the whole animal model is the most traditional pharmacological screening model and is crucial to the evaluation of medicines. Even though this approach is expensive and inefficient, it is still the mainstay for drug evaluation and discovery today. There are numerous in vivo and in vitro techniques for pharmacological screening of medicinal plants with immunomodulatory properties.

Methods in vitro:

1. Prevention of mast cells from releasing histamine
2. Lymphocyte proliferation caused by mitogens
3. Prevention of the growth of T cells
4. The ability of macrophages to glow
5. Plaque-forming colony (PFC) test in vitro
6. Stunting dihydro-orotate dehydrogenase

Methods in vivo:

1. Animals' autoimmune illnesses that develop on their own
2. In rats, acute systemic anaphylaxis
3. Anti-anaphylactic action (response of Schultz-Dale)
4. Anaphylaxis of the passive skin
5. Arthus-type hypersensitivity that occurs instantly
6. Type I hypersensitivity
7. Arthus reaction in reverse passive
8. In rats, adjuvant arthritis
9. Arthritis caused by collagen type II in rats
10. Mice with progressive polyarthritis caused by proteoglycan
11. Thyroiditis with experimental autoimmune
12. Coxsackievirus B3-induced myocarditis
13. Autoimmune disease caused by porcine cardiac myosin [11].

IMMUNOMODULATION BY MEDICINAL PLANTS:

Withania somnifera:

Babl/c mice's immune systems were shown to be stimulated when an extract from the powdered root of the herb Withania somnifera was administered. Five doses of Withania root extract (20 mg/dose/animal; i.p.) were administered, and on the tenth day, the overall WBC count (17125 cells/mm(3)) increased. Both the alpha-esterase positive cell number (1800/4000 cells) and bone marrow cellularity (27x10(6) cells/femur) rose significantly ($P<0.001$) following the administration of Withania extract. When the antigen (SRBC) and Withania extract were administered together, the circulating antibody titre and the quantity of

plaque-forming cells (PFC) in the spleen increased. The fourth day yielded the highest quantity of PFC (985 PFC/10(6) spleen cells). In mice, withania extract prevented the delayed type hypersentivity response (Mantoux test). When compared to control (31.5/200 cells), administration of withania extract also increased the phagocytic activity of peritoneal macrophages in mice (76.5 pigmented cells/200). These findings support the immunomodulatory properties of W. somnifera extract, a well-known immunomodulator in traditional medicine [12].

Morus alba Linn. (Mulberry):

The conventional medication was Ocimum sanctum (100 mg/kg, po), while the methanolic extract of Morus alba was given orally at low and high doses of 100 mg/kg and 1 g/kg, respectively. It significantly improved the phagocytic index in the carbon clearance assay, significantly prevented neutropenia caused by cyclophosphamide, and enhanced neutrophil adhesion in the neutrophil adhesion test. It was therefore determined that Morus alba boosts humoral immunity as well as cell-mediated immunity [13].

Sophora subprosrate:

According to the findings, SSP1 increased the number of murine splenic lymphocytes and their production of IFN-gamma at in vitro doses of 50, 100, 200, or 400 mg/L. Tumor necrosis factor-alpha and interleukin-6 levels were elevated by SSP1 in immunocompromised mice that received a subcutaneous injection of 1.25 mg/kg of dexamethasone. When SSP1 was administered intraperitoneally, the spleen index, glutathione level, and lysozyme and glutathione peroxidase activities in immunocompromised mice [14].

Acacia catechu:

An increase in neutrophil adherence to nylon fibers, a notable rise in the phagocytic index, and a notable defense against cyclophosphamide-induced neutropenia were all demonstrated by Acacia catechu extract, suggesting that it has an impact on cell-mediated immunity. However, the extract from Acacia catechu significantly raised the serum immunoglobulin levels, raised the haemagglutination titre values, and reduced the mortality ratio in mice, indicating that it had an impact on the humoral arm of the immune system. It was determined from the aforementioned data that Acacia catechu aqueous extract significantly influences humoral and cell-mediated immunity [15].

Jatropha curcas L :

It was established how an 80% aqueous methanol extract (AME) and compounds 1–5 (0.25 mg/kg body weight) affected the immune system of one-day-old specified pathogen-free (SPF) chicks. There was evidence of both humoral and cell-mediated seroresponse stimulation. Significantly high levels of macrophage, lymphocyte, and antibody titers were observed in the blood [16].

Achillea wilhelmsii:

In female Swiss albino mice, the immunomodulatory effects of aqueous extract of Achillea wilhelmsii (25, 50, and 100 mg/kg body weight for 5 days) were assessed based on body weight, relative organ weight, delayed type of hypersensitivity (DTH) response, and haemagglutination titre (HT). No discernible variations in body weight growth were found among the animal groups. At 100 mg/kg, a notable rise in the spleen's relative organ weight was noted. There was no increase in kidney relative weight or liver function test (LFT) enzyme levels in the studied plant dosages. The DTH response

was significantly increased by the A. Wilhelmsii extract at a concentration of 100 mg/kg [17].

Picrorhiza Scrophulariiflora:

The methanol extract of Picrorhiza scrophulariiflora contains a glycoside called scrocaffeside A, which by structure has immunomodulatory qualities. The scrocaffeside A increased splenic cell proliferation and responsiveness to lipopolysaccharide (LPS) and polyclonal T cell mitogen concanavalin A (Con A). The activity of natural killer cells and peritoneal macrophages was likewise significantly increased upon administration of scrocaffeside A at dosages ranging from 5 microg/ml to 125 microg/ml. A dose-dependent rise in mature T cell subgroup populations was also noted.The CD4/CD8 population of splenocytes and cytokine production were both increased. After being treated to scrocaffeside A, cultured splenocytes' expression of interleukin (IL)-2, IL-4, IL12, and (IFN)-gamma rose noticeably. It appears from these findings that scrocaffeside A may have immune-boosting properties. It may develop into a novel immunostimulating agent in the future in addition to its historical application in a few illnesses [18].

Picrorhiza Scrophulariiflora:

One glycoside (scrocaffeside A,) from the methanol extract of Picrorhiza scrophulariiflora, shows immunomodulatory properties by structure. The scrocaffeside A enhanced proliferation of splenocytes and their response to polyclonal T cell mitogen concanavalin A (Con A) and lipopolysaccharide (LPS). There was also a significant increase in the activity of peritoneal macrophages and natural killer cell when treated with doses of scrocaffeside A between 5 microg/ml and 125 microg/ml. A dose-dependent increase was also observed in the populations of mature T cell subsets. The production of cytokines and the CD4/CD8 population of splenocytes were also elevated. The levels of interleukin (IL)-2, IL-4, IL12, and (IFN)-gamma expressed by cultured splenocytes were significantly increased when the cells were exposed to scrocaffeside A. These results indicate that scrocaffeside A may exert immunoenhancement effects on immune system. In addition to its traditional use in some diseases, it may become a new immunostimulating agent in the future [19].

Plantago asiatica L.:

The seeds of Plantago asiatica L. were often used as a traditional Chinese medicine for some immunologically weak patients suffering from chronic illness. These uses could be related to immunomodulatory properties of the plant. AIM OF THE STUDY: In this study, effects of extract of the seeds of Plantago asiatica L. (ES-PL) were investigated on the maturation of dendritic cells (DCs), which play significant role in primary immune system [20].

Panax ginseng:

Ginsenosides, the plant's active ingredients, may be essential to the variety of physiological effects of ginseng, which is thought to have positive effects against human illnesses. It is still necessary to look into the mechanisms underlying ginseng's benefits. We make some biological The anti-inflammatory properties of ginseng are what give it its effects. After being stimulated by TNF-alpha, 70% ethanol-water extracts of ginseng markedly reduced the transcription and release of CXCL-10. HPLC analysis of our extract revealed the presence of nine ginsenosides, including Rb1, Rb2, Rc, Rd, Re, Rf, Rg1, Rg3, and Rh1 [21].

Caesalpinia bonducella:

The evaluation of immunomodulatory potential by oral administration of ethanolic seed extract of Caesalpinia bonducella (200-500 mg/kg) evoked a significant increase in percent neutrophil adhesion to nylon fibers as well as a dose-dependent increase in antibody titre values, and potentiated the delayed-type hypersensitivity reaction induced by sheep red blood cells. Also it prevented myelosuppression in cyclophosphamide drug treated rats and good response towards phagocytosis in carbon clearance assay [22].

Garlic (Allium sativum):

An significant therapeutic spice, garlic (Allium sativum) has a wide range of biological actions, including immunomodulation. The identities of some of the garlic's immunomodulatory proteins remain unclear despite their description. Isolating immunomodulatory proteins from raw garlic and analyzing their impact on specific immune system cells (lymphocytes, mast cells, and basophils) in connection to mitogenicity and hypersensitivity were the goals of the current work. Three 13 kD protein components (QR1, QR-2, and QR-3 in a 7:28:1) were isolated using Q-Sepharose chromatography of a 30 kD raw garlic extract ultrafiltrate. Regarding human peripheral blood lymphocytes, murine splenocytes, and thymocytes, all three proteins demonstrated mitogenic activity [23].

Cynodon dactylon:

The grass's fresh juice was made according to traditional medical guidelines and standardized for solid content. Using the Folin-Ciocalteau method, its total phenol content was calculated. In vitro, the impact of freshly made juice on doxorubicin-induced DNA damage was studied. By measuring the humoral antibody response using the spleen cell assay and haemagglutination antibody titer, its immunomodulatory function was assessed in balb/c mice [24].

CONCLUSION

Medicinal plants have long been integral to traditional healthcare systems for the prevention and treatment of diseases associated with immune dysfunction. The evidence reviewed demonstrates that many of these plants possess significant immunomodulatory properties capable of stimulating or suppressing specific immune pathways. Compounds derived from plants such as *Withania somnifera*, *Panax ginseng*, and *Picrorhiza scrophulariiflora* modulate cytokine release, antibody formation, and macrophage activity, thus influencing both humoral and cell-mediated immunity. Given the limitations of conventional immunotherapies, including high cost and side effects, herbal immunomodulators represent a promising, accessible alternative for restoring immune balance. However, further research is essential to isolate active constituents, elucidate molecular mechanisms, and conduct controlled clinical trials to ensure efficacy, safety, and standardization. Harnessing these traditional remedies through modern pharmacological validation could lead to the development of next-generation immunotherapeutic agents derived from natural sources.

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HOW TO CITE: Sujata Kshirsagar, Immunomodulatory Medicinal Plants, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 2, 2100-2107. https://doi.org/10.5281/zenodo.18628909