

Review Article

Role of Medicinal Plants as Immunostimulants in Health and Disease

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Abstract

Complementary and alternative medicine involves the use of herbs and medicinal plants as an alternative to mainstream western medical treatment. A large number of Indian medicinal plants have been reported to possess immunostimulant activity and thus can serve as potential source of drug in various immunocompromised states including AIDS, cancer and for treatment of various chronic infections. This review describes role of plant derived Immunostimulants in health care.

INTRODUCTION

The immune system evolved to discriminate self from nonself. Immunity may be defined as the body's ability to identify and resist large number of infectious and harmful microorganisms, enabling the body to prevent or resist diseases and inhibit tissue damage. Immune system mediated diseases are significant medical problems. Immunological diseases are rapidly growing that require aggressive and innovative approaches to develop new treatments. These diseases include various autoimmune diseases such as rheumatoid arthritis, type I diabetes mellitus, systemic lupus erythematosus, multiple sclerosis, hematological malignancies, infectious diseases, asthma, various allergic conditions, inflammatory bowel diseases, glomerulonephritis, thrombocytopenia, myasthenia gravis, polyarteritis, Behcet's syndrome, uveitis and immune system mediated graft rejection [1]. Two arms of immunity (innate and adaptive) work closely together. Innate immune system is most active early in an immune response and adaptive immunity becoming progressively dominant over time. The major effectors of innate immunity are complement, granulocytes, monocytes/macrophages, natural killer cells, mast cells and basophils. The major effectors of adaptive immunity are B & T lymphocytes. These cells are important in normal immune response to infection and tumors, but also mediate transplant rejection and autoimmunity [1].

Immunomodulators are biological or synthetic substances that can stimulate suppress or modulate any aspect of the immune system [2]. Clinically Immunomodulators can be classified into 3 categories. Immunoadjuvants are used to enhance efficacy of vaccines and could be considered specific immune stimulants. They hold the promise of being the true modulators of the immune response. Immunosuppressants are a structurally and functionally heterogeneous group of drugs

which are generally given in combination regimens to treat various autoimmune diseases and to prevent transplant rejection. Immunostimulants are inherently nonspecific and enhance body's resistance to infection. They can act through innate as well as adaptive immune responses in healthy volunteers; Immunostimulants are expected to serve as prophylactic and promoter agents. In immunocompromised patients they are expected to act as immunotherapeutic agents. These agents are used to treat serious infections, immunodeficiency and cancer [2]. Both Immunosuppressants and stimulants have serious side effects; Complementary or traditional remedies are other options to overcome this problem. Herbal medicine (traditional or natural medicine) has always existed in one way or another in different cultures and civilizations such as Ayurvedic (India), Western, Chinese, Kampo (Japan) and Greco-Arab or Unani-Tibb (South Asia). Traditional medicine all over the world is currently being evaluated through extensive research activity on various plant species for their potential therapeutic effects. The Ayurvedic system of medicine is one of the oldest systems of medicine and includes ethnopharmacological activities such as immunostimulation, immunosuppression, tonic, antiageing, antirheumatic, anticancer adaptogenic, antistress and Rasayana etc [3]. An entire section of the Materia Medica of Ayurveda is devoted to Rasayana (drugs reputed to enhance body resistance). A number of medicinal plants as Rasayanas have been claimed to possess immunomodulatory activities [4]. There is a long list of plant products which possess immunostimulatory and immunosuppressive activity and these products are in use for the treatment of various immunocompromised conditions including HIV infections and autoimmune diseases by Ayurvedic practitioners. This review describes only medicinal plants possessing immunostimulant activity.

***Asparagus racemosus* Wild (family Asparagaceae, Liliaceae) Hindi name – Satawar, English name – Wild asparagus**

The protective effect of *A. racemosus* against myelosuppression induced by single dose (200 mg/kg, sc) cyclophosphamide to mice has been reported by Thatte & Dahanukar 1988 [5]. *A. racemosus* itself produced leucocytosis and neutrophilia but when compared with control group, *A. racemosus* prevented leucopenia produced by cyclophosphamide. These workers suggested that *A. racemosus* is a potent immunostimulant with effects comparable to lithium and glucan. In animal models of intraperitoneal adhesions, *A. racemosus* prevent postoperative adhesions [6] Dhuley [7] (1997) reported that *A. racemosus* treatment significantly inhibited carcinogen ochratoxin-A induced suppression of chemotactic activity and production of IL-1 and TNF- α by mouse macrophages. *A. racemosus* induced excess production of TNF when compared with control.

***Aloe vera* Linn Burm F. (family – Liliaceae) Hindi name – Ghrita Kumari, English name – Indian Aloe**

Acemannan (a carbohydrate fraction from gel of *A. vera*) has been shown to increase production of IL-1 and TNF- α from peripheral macrophages [8]. It also induces nitric oxide (NO) release, expression of surface molecules and morphologic changes in mouse macrophage cell line (RAW 264.7) [8] Macrophage activation may be accountable for immunostimulating effects of acemannan [9]. Acemannan may be responsible for regression of tumors in experimental animals and increased lymphocyte response to alloantigen via IL-1 production. Oligosaccharides from *A. vera* may prevent ultraviolet induced suppression of delayed type hypersensitivity by reducing keratinocyte derived immunosuppressive cytokines [10]

***Allium sativum* (family Liliaceae) Hindi name – Lasun, English name -Garlic**

Garlic extracts particularly organosulfur compounds have been shown to inhibit growth of tumors in animals probably by activation of natural killer (NK) cells, stimulation of T lymphocytes and enhanced production of IL-2 [11] Morioka et al reported that garlic extract enhance cytotoxicity of human peripheral blood lymphocytes against both NK cell sensitive (K562) and resistant (M14) cell lines [12] Lau et al have demonstrated that garlic may augment macrophage and T lymphocyte functions [13] Garlic extract prevented from ultraviolet induced suppression of contact hypersensitivity [14]

***Azadirachta indica* A. Juss (family Meliaceae) Hindi name – Neem, English name – Margosatree**

Recent studies have shown that *A. indica* possess nonspecific immunostimulatory properties [15] In mice intraperitoneal injection of neem oil mobilizes leukocytic cells into peritoneal cavity. Peritoneal macrophages exhibited enhanced phagocytic activity and MHC class II expression. Spleen cells of neem oil treated mice showed higher lymphocyte proliferative response to concanavalin A and tetanus toxoid compared to control. Treatment of mice splenocytes with *A. indica* stimulates production of IL-1, interferon- γ - and TNF- α , reflecting activation

of Th1 type of response [16]. Significant reduction in erythema, desquamation and infiltration of psoriatic lesions in patients treated with *A. indica* leaf extract (300 mg/day in 3 divided doses) has also been reported. This indicates immunostimulatory properties of *A. indica* [17] Sai Ram et al [18] have demonstrated immunomodulatory properties of NIM-76, a volatile fraction from *A. indica*. In rats NIM-76 single intraperitoneal injection resulted in increase in polymorphonuclear leukocytes with decrease in lymphocyte count in blood. At 120 mg/kg, there was enhanced macrophage activity and lymphocyte proliferation response. At higher doses (300mg/kg) there was stimulation of mitogen-induced lymphocyte proliferation. Study indicates that NIM-76 primarily acts through cell mediated mechanisms by activating macrophages and lymphocytes.

***Andrographis paniculata* Burn F. (Family Acanthaceae) Hindi name – Charayata, Kalmegh, English name – Bhunimba**

Ethanol extract and diterpene andrographolides from *A. paniculata* have been shown to induce significant stimulation of antibody and delayed type hypersensitivity response to sheep red blood cells in mice [19] There is stimulation of macrophage migration, phagocytosis of 14C leucine labelled E. coli and in vitro proliferation of splenic lymphocytes [19] The stimulation was found to be both antigen specific and non-specific. It was lower with purified andrographolides than with ethanol extract indicating presence of other substances other than andrographolides which may be responsible for immunostimulation. Andrographolide from *A. paniculata* inhibited the induction of NO synthase by lipopolysaccharide in RAW 264.7 cells [20].

***Abutilon indicum* Linn (Family Malvaceae) Hindi name – Jhampi, Kanghi, English name – Indian Hallow**

Essential oil from this plant augments antibody in animals showing immunological value [21].

***Cynodon dactylon* Linn (family Poaceae) Hindi name – Dub, Durva, English name – Creeping panic grass, Devil's grass**

A perennial creeping herb, common all over India. Distributed throughout Burma, Sri Lanka, Australia, America and warm countries. Fresh extract of *cynodon dactylon* investigated clinically in 10 patients of idiopathic thrombocytopenic purpura, gave remissions for a longer period of time. Durva also controlled haematuria in a few patients. In patients with bone marrow depression, it increased the platelet count and white blood cells. The drug was safe and had no side effects [22]

***Curcuma longa* (family Zingibaraceae) Hindi name – Haldi, English name – Turmeric**

Turmeric has been reported to increase mitogenic responses of splenic lymphocytes [23] Japanese investigators have isolated a polysaccharide (Ukonan A-D) which stimulates carbon clearance [24]. They have also isolated a lipopolysaccharide from the root of *C. longa* which is immunostimulant [25]. Dietary curcumin (40 mg/kg) in rats for 5 weeks enhanced IgG levels but did not affect delayed type hypersensitivity and NK cell activity. Curcumin inhibits NO production in activated macrophages [26]. The anticancer properties of curcumin may be mediated at least in part by inhibition of inducible form of NO synthase.

***Embelia ribes* Burm (Family – Myrsinaceae) Hindi name – Vayavidanga, English name – Embelia.**

A large scandant shrub found throughout India, from Central Himalaya to Konkan, Deccan, Western Ghats and South India. Preliminary pharmacological studies demonstrated immunostimulant activity of this plant [27].

***Nuctanthes arbor-tristis* Linn (Family Oleaceae) Hindi name – Harsinghar, Saherwa , English name – Night Jasmine.**

A hardy large shrub or small tree, native of India. Puri et al 1994 [23]. Demonstrated immunostimulant activities from this plant extract. Stimulation of antigen specific and nonspecific immunity as evidenced by increase in humoral and delayed type hypersensitivity response and macrophage migration has been demonstrated in mice treated with 50% ethanol seed extract [28].

***Ocimum sanctum* Linn. (Family – Labiatae) Hindi name – Tulsi, English Holy basil.**

Radioprotective effect of *O. sanctum* leaf extract in combination with WR-2721 has been reported [29] *O. sanctum* (10 mg/kg, ip) for 5 days were given to mice or 100 to 400 mg/kg WR-2721 or combination of the two, and whole body was exposed to 4.5 or 2 Gy gamma radiation. Protective effect of water extract (10 mg/kg/day) was more than the aqueous-ethanol extract in protecting mice against 11 Gy of Co-60 gamma irradiation [30]. Efficacy of *O. sanctum* crude extract was compared with dexamethasone in the treatment of patients with acute viral encephalitis. The survival in *O. sanctum* treated group was significantly higher [31].

***Piper longum* Linn (Family Piperaceae) Hindi name – Pippali, English name – Indian long pepper.**

A slender, aromatic, climber with perennial woody roots occurs in hotter parts of India from Central Himalayas to Assam, Khasi and Mikir Hills, Bengal, Western Ghats from Konkan to Travancore. Some clinical trials were carried out with fruit extract of *P. longum* in patients with asthma, chronic sinusitis, giardiasis and for antifertility properties.

Agarwal & Kaul (1992) [32] reported radioprotective effect of piperine alkaloid from *P. longum*. Tripathi et al (1999) [33] demonstrated immunostimulatory effect of *P. longum* fruit extract.

***Panax ginseng* (Family Araliaceae)**

P. ginseng is widely used as general health tonic. Extracts and saponins from Indian Pseudoginseng have been shown to possess potent immunostimulant activity. Fractions of ginseng extract have been reported to possess stimulatory activity on reticuloendothelial system, T-cell proliferation by Con A in vitro [34], Phagocytosis [35], chemotaxis, augmentation of NK cell activity [36], enhancement of antibody forming plaques and haemagglutinating antibody titers against Sheep Red Blood Cells (SRBC) [37], production of IL-1 [36], IL-2 [36], TNF- α , GM-CSF [36], increase in population of CD₃, CD₄ and CD₈ cells. Ginseng appears to be a promising agent to be evaluated for immunostimulatory activity in humans.

***Punica granatum* Linn (family Punicaceae) Hindi name – Anar, English Name – Pomegranate.**

Aqueous suspension of the fruit rind powder to rabbit (100 mg/kg, po) stimulated the cell mediated and humoral components of immune system. There was an increase in antibody titer to typhoid H. antigen. It also enhanced the inhibition of leukocyte migration in leukocyte migration inhibition test and in duration of skin in delayed hypersensitivity test with purified protein derivative [38].

***Picrorhiza kurroa* (Family Scrophulariaceae) Hindi name – Kutaki, English name – Picrorhiza**

Ethanol extract from *P. kurroa* has been shown to enhance delayed type hypersensitivity by 80% and also antibody production and phagocytic activity *P. kurroa* (50% ethanol extract) produced dose dependent increase in SRBC induced early and delayed hypersensitivity reaction in mice and rats. It also enhanced humoral immune responses in mice and rats and phagocytic function of reticuloendothelial cells in mice [39]. It augmented responsiveness of murine splenocytes to T cell mitogens (Phytohaemagglutinin and Con A & B, LPS) [39]. Picroliv isolated from *P. kurroa* given to mice before immunization with SRBC, resulted in significant increase in haemagglutinating antibody titer, plaque forming cells and delayed type hypersensitivity response [40]. It also increased macrophage migration, ¹⁴C leucine labelled *E. coli*, Chemiluminescence of peritoneal macrophages and higher uptake of ³H-thymidine in lymphocytes of picroliv treated mice.

***Phyllanthus emblica* Linn (Family – Euphorbiaceae) Hindi name – Amla, English name – Indian Gooseberry**

P. emblica fruit powder was found to enhance NK cell activity and antibody dependent cellular cytotoxicity in Syngenei Bal B/c mice fearing Dalton's lymphoma ascites tumor [41]. There was 35% increase in life span in tumor bearing mice treated with *P. emblica* as compared to controls.

***Saussurea costus* (Falc) (Family-Asteraceae) Hindi name – Kuth, English name – Kuth.**

Preliminary pharmacological studies reported immunostimulant properties from the plant extracts [41].

***Sida cordifolia* Linn (Family – Malvaceae) Hindi name – Kungyi, English name – Country mallow.**

Ghosal et al [43] reported immunostimulant activity of sitoindosides fractions from *S. cordifolia*.

***Tinospora cordifolia* Wild, *T. sagittata*, *T. malafarica* (Family – Menispermaceae), Hindi name – Giloe, English name – Gulancha tinospora**

Oral administration of *T. cordifolia* extract to mice for 15 days significantly enhanced humoral immune response [44] Protective effect of *T. cordifolia* against myelosuppression induced by cyclophosphamide in rats has been demonstrated. Thatte et al (1994) [45] reported that *T. cordifolia* (100 mg/kg/day \times 10 days) activates macrophages to release GM-CSF activity. *T. cordifolia* water extracts (100 mg/kg/day \times 7 days)

improved cellular immune functions. Mortality rate following *E.coli* infection in treated rats was significantly reduced (16.7%). Treatment with *T. cordifolia* inhibited ochratoxin induced suppression of chemotactic activity and production of IL-1 and TNF- α by mouse macrophages. Syringin (TC-4) and Cardiol (TC-7) isolated from *T. cordifolia* significantly increased IgG antibodies in serum. Humoral and cell mediated immunity were also found to be increased. Macrophage activation has been reported by cordioside (TC-2), Cordiofolioside A (TC-5) and Cardiol (TC-7) [46].

***Withania somnifera* (L) Dunal (Family – Solanaceae)**
Hindi name – Ashwagandha, English name – Winter Cherry

A number of withanolides isolated from *W. somnifera* have been shown to possess both immunostimulating and immunosuppressive properties. Methanolic extract was found to increase total WBC count in normal Balb/C mice and in mice with leucopenia induced by sublethal dose of gamma irradiation [46]. Ashwagandha prevented myelosuppression in mice induced by cyclophosphamide, prednisolone and azathioprin. Treatment with ashwagandha inhibited ochratoxin A induced suppression of chemotactic activity and production of IL-1 and TNF- α by macrophages [47]. A dose of 30 mg/kg of Withaferin A significantly enhanced the spleen colony forming unit (CFU-S) in irradiated (2 GY whole body gamma irradiation) animals [48].

***Mangifera indica* Linn (Family – Anacardiaceae)**
Hindi name – Aam, English name – Mango tree.

Alcoholic extract of the stem bark of *M. indica* (containing 2.6% mangiferin) produced an increase in humoral antibody titer and delayed type hypersensitivity in mice [49].

Many other plants have been shown to possess immunostimulant properties in animal tests [3] include *Abrus precatorium*, *Albizia lebeck*, *Aristolochia indica*, *Clitoria ternatea*, *Catharanthus roseus*, *Cymbopogon martini*, *Hyoscyamus niger*, *Nordostachys jatamansi*, *Terminalia belerica*.

DISCUSSION AND CONCLUSION

Therefore, many Indian medicinal plants possess immunostimulant properties and they can serve as a potential source for drugs for various immunocompromised states including AIDS, cancer and for the treatment of serious chronic infections. However, before subjected to clinical study, there is need for isolation of pure active ingredients, their chemical characterization and standardization of herbal product, so that these compounds may be evaluated for clinical use.

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