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, anti rheumatic, 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 – Sataraw, 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 [6] Dhuley [7] (1997) reported that immunosuppressive cytokines [10] response to alloantigen via IL-1 production. Oligosaccharides of tumors in experimental animals and increased lymphocyte acemannan [9]. Acemannan may be responsible for regression in mouse macrophage cell line (RAW 264.7) [8] Macrophage peripheral macrophages [8]. It also induces nitric oxide (NO) has been shown to increase production of IL-1 and TNF-α from itself produced leucocytosis and neutrophilia but racemosus mice has been reported by Thatte & Dahanukar 1988 [5]. *A. racemosus* induced 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 slower 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 atleast in part by induction of inductive form of NO synthase.
Embelia ribes Burm (Family - Myrsinaceae) Hindi name - Vayavidanga, English name - Embelia.

A large scandent 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 WR-2721 has been reported [29].

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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 crude extract of P. longum in patients with asthma, chronic sinusitis, giardiasis and for antifertility properties.


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 CD4, CD8 and CD19 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 [30].

Picrorhiza kurroa (Family Scrophulariaceae) Hindi name - Kutaki, English name - Picrorhiza

Ethanolic 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 delay type hypersensitive 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 BALB/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 sitionoindolides 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 × 10 days) activates macrophages to release GM-CSF activity. T. cordifolia water extracts (100 mg/kg/day × 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), Cordifolioside A (TC-5) and Cordil (TC-7) [46].

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

A number of with anolides isolated from W. somnifera have been shown to possess both immunostimulating and immunosuppressive properties. Methanol 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 lebbeck, Aristolochia indica, Clitoria ternatea, Catharanthus roseus, Cymbopogon martini, Hyoscyamus niger, Nordostachys jatamansi, Terminalia bellerica.

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.

REFERENCES


