Phcog Rev.: Review Article

Immunomodulatory Plants: A Phytopharmacological Review

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ABSTRACT
Since ancient times, plants have been an exemplary source of medicine. Ayurveda and other Indian literature mention the use of plants in treatment of various human ailments. India has about 45,000 plant species and among them, several thousands have been claimed to possess medicinal properties. There are many plants which are having immunostimulatory whereas other have immunosuppressant activity. The present paper review plants which have shown experimental and clinical immunomodulatory activity.

KEYWORDS: Herbal plants, immunomodulation, phytochemistry, pharmacology.

INTRODUCTION
The term “immunomodulation” denotes a change, a strengthening of suppression, of the indicators of cellular and humoral immunity and nonspecific defense factors. The essence of immunomodulation is that a pharmacological agent acting under various dose and time regimens displays an immunomodulating effect (1, 2). The immunomodulating action is reversible and requires maintaining the dose of a preparation. The extreme manifestations of immunomodulating action of biologically active substances are immunosuppression (depression of the immune response) and immunostimulation (immunopotentiation or strengthening of the immune reactions) (3). Hence both immunostimulating agents and immunosuppressing agents have their own standing and search for better agents exerting these activities is becoming the field of major interest all over the world (4). Natural adjuvants, synthetic agents, antibody reagents are used as immunosuppressive and immunostimulative agents. But there are major limitation to the general use of these agents such as increased risk of infection and generalized effect throughout the immune system (5). Traditional Indian system of medicines like Siddha and Ayurveda has suggested means to increase the body’s natural resistance to disease. A number of Indian medicinal plants and various ‘rasayanas’ have been claimed to possess immunomodulatory activity (5, 6). In this review we will focus on the various immunomodulators from plant origin.

IMMUNOMODULATORY PLANTS

Aloe vera
Aloe vera (L.) Burm.f. (Family: Aloeaceae, Formerly in the Liliaceae family). The true aloe vera plant is called Aloe barbadensis Miller, otherwise called the Curacao aloe, and is the most medicinally potent of the 300 (and more) varieties found around the world. Two new dihydrocoumarin derivatives have been isolated from Aloe vera and their structures had been determined by X-ray crystallographic diffraction analysis and extensive 1D, 2D NMR spectroscopic data. Both of them evidently showed antioxidant activity against superoxide and hydroxyl radicals. Only compound 1 exhibited immunomodulatory activity in relation to increasing the phagocytic activity and stimulating the production of superoxide anions in the oxygen respiratory burst of rat peritoneal macrophages (7).

Andrographis paniculata
Andrographis paniculata is traditionally known as kalmegh belongs to family Acanthaceae and is widely used in Ayurvedic and Homeopathic systems of medicine. Several active components have been identified, two of which are andrographolide and neandrographolide. The primary medicinal component of Andrographis is andrographolide. It has a very bitter taste, is a colorless crystalline in appearance, and is called a “diterpene lactone” Both of these compounds are reported to have bactericidal activity (8). Mice studies have shown that Andrographis paniculata is a potent stimulator of the immune system in two ways: (1) Antigen-specific response: antibodies are made to counteract invading microbes, and (2) Nonspecific immune response: macrophage cells scavenge and destroy invaders. Andrographis paniculata activates both responses - making it effective against a variety of infectious and oncogenic (cancer-causing) agents. These and other related compounds present in andrographis also appear to have immunostimulatory properties and anti-inflammatory properties via adrenal activity (9, 10). Preliminary evidence suggests that the use of an extract of andrographis may help to reduce the intensity and duration of the common cold. In one study, patients taking andrographis showed significant improvement in symptoms compared to those taking placebos (10). In addition andrographis extracts from the leaves of the plant are also cytotoxic (cell-killing) against cancer cells (11). This cancer cell-killing ability was demonstrated against human epidermoid carcinoma (squamous cell carcinoma) of the skin lining of the nasopharynx and against lymphocytic leukemia cells (12). It was the andrographolide component that was found to have the cancer cell-killing ability.
Asparagos racemosus
Immunomodulating property of Asparagos racemosus (Liliaceae) has been shown to protect the rat and mice against experimental induced abdominal sepsis (13, 14). Oral administration of decoction of powdered root of A. racemosus has been reported to produce leucocytosis and predominant neutrophilia along with enhanced phagocytic activity of the macrophages and polymorphs. Percentage mortality of A. racemosus treated animals was found to be significantly reduced while survival rate was comparable to that of the group treated with a combination of metronidazole and gentamicin (13, 14). Since A. racemosus is reported to be devoid of antibacterial action, so protection offered by it against sepsis by altering function of macrophages, indicates its possible immunomodulatory property (13). Further, oral administration of total extract of A. racemosus has been shown to reduce all the three attributes viz. number, character and area markedly in an animal model of intraperitoneal adhesions (15). Dhuley (16) has reported the revival of macrophage chemotaxis and interleukin-1 (IL-I) and tumor necrosis factor a (TNF-a) production by the oral treatment of A. racemosus root extract in ochratoxin a treated mouse. Alcoholic extract has been found to enhance both, humoral and cell mediated immunity of albino mice injected with sheep red blood cells as particulate antigen (17).

Azadirachta indica
Azadirachta indica (Meliaceae) commonly known as Neem is a powerful immunity Booster. Neem also boosts the body's macrophage response, which stimulates the lymphocytic system, and boosts production of white blood cells. Neem oil acts as a non-specific immunostimulant and that it selectively activates the cell-mediated immune mechanisms to elicit an enhanced response to subsequent mitogenic or antigenic challenges (18). Immunostimulant activity: The aqueous extract of neem bark possesses anticomplement activity, acting both on the alternative as well as the classical pathway of complement activation in human serum (19). Recently, an aqueous extract of stem bark has been shown to enhance the immune response of Balb-c mice to sheep red blood cells in vivo (20). Leaf extract at 100 mg/kg after three weeks of oral administration causes higher IgM and IgG levels along with increased titer of antiovalbumin antibody (21). Neem oil has been shown to possess immunostimulant activity by selectively activating the cell-mediated immune mechanisms to elicit an enhanced response to subsequent mitogenic or antigenic challenge (22). NIM-76, a fraction isolated from Neem oil, has immunomodulatory properties. The initial response of NIM-76 treatment appears to be a stimulation of PMN counts, activation of macrophages (increased phagocytosis and NBT reduction), and promotion of T-lymphocyte proliferative responses(23). Crude neem oil after i.p. administration into the mice stimulated the T cells to produce gamma-IFN which in turn stimulate macrophage(24).

Boerhiva diffusa
Boerhaavia diffusa Linn. (Nyctagninaceae) is a small perennial creeping herb, commonly known as “Red hogweed” and distributed widely all over in India, and in many other countries. The plant is known to possess immunomodulatory activities (25, 26). The alkaloidal fraction of Boerhiva diffusa significantly restored the suppressed humoral response in stressed rats wherein Boerhiva diffusa increased the suppressed antibody titres following immunization by sheep RBCs in rats subjected to restraint stress (27). It also significantly reversed the depleted adrenal cortisol level and the elevated plasma cortisol level in the stressed rats, thus appearing to have a corticosteroid sparing effect in experimental stress.

Camellia sinensis
Immunomodulatory effects also have been observed with aqueous extracts of the tea, Camellia sinensis, as they slightly enhance neopterin production (a sensitive marker of Cell-Mediated Immunity) in unstimulated human peripheral mononuclear cells in vitro, whereas a reduction of neopterin formation is seen in cells stimulated with mitogens (28).

Centella asiatica
Centella asiatica (Aipicaceae) is a perennial creeper, growing abundantly in moist areas and distributed widely in tropical and subtropical countries. In India, it is called “Mandukaparani” and used in folk medicine for leprosy, lumps, syphilis, and tuberculosis and to improve mental function (29), and is also used in rasayanas (30). The reticuloendothelial stimulating activity of the alcoholic extract of C. asiatica (31) and an increase in the antibody titer and cell-mediated response (DTH) at 100 mg/kg body wt. of dried powdered of C. asiatica have been reported (32). Asiaticoside is the major constituents of C.asiatica (33).

Clausena excavata
Clausena excavata a wild shrub of the Rutaceae family is widely distributed in Southern Asia (34). Many phenolics compounds such as furanocoumarins, flavonoids and carbazole alkaloids from aqueous of C. excavata have been isolated (35, 36). They have been previously shown to stimulate or suppress the immune system affecting an enzymatic system as the electron-transferring system resulting in an immunomodulating property, especially on phagocytic activity (37). The immunomodulating activity observed in these fractions might be ascribed to the presence of phenolics hydroxyl groups or to other molecular moiety. C. excavata wood may contain components which had immunomodulatory activity on mouse immune system. The fractions eluted from the aqueous hot extract and acetone extract seem to be the most active (38).

Curcuma Longa
Turmeric is the dried rhizome powder of Curcuma longa, a perennial herb of the Zingiberaceae family. The major chemical principles of turmeric are curcuminoids, which impart characteristic yellow color to it. The curcuminoids can be separated from turmeric by ethanol extraction and it usually contains 0.3-5.4% curcumin (one of the major curcuminoids) depending on the season of its harvest (39). Vogel and Pellatier (40) first reported molecular formula of curcumin as C_{15}H_{20}O_{6}, which was later identified as diferuloylmethane (40). The IUPAC name of curcumin is (1,7-bis (4-hydroxy-3-methoxy-phenyl) hepta-1, 6-diene-3, 5-
Echinacea is one of the most highly regarded immune system stimulants. Numerous lines of evidence suggest that curcumin can modulate both the proliferation and the activation of T cells. Curcumin inhibited the proliferation induced by concanavalin A (Con A), phytohemagglutinin (PHA), and phorbol-12-myristate-13-acetate (PMA) of lymphocytes derived from fresh human spleen. In another study, curcumin inhibits the proliferation induced by PMA and anti-CD28 antibody or that induced by PHA of T lymphocytes isolated from healthy donors. Yadav et al. also reported that curcumin can suppress the PHA-induced proliferation of human peripheral blood mononuclear cells (PBMCs) and inhibit IL-2 expression and NF-κB. In still another report, curcumin inhibited the activation of human V γ T cells induced by phosphoantigens (45). Effect on B cells Inhibits Epstein bar virus-induced B-cell proliferation and immortalization. Increases B-cell proliferation in intestinal mucosa of mice.

Desmodium gangeticum

Desmodium gangeticum (Leguminosae) is a small perennial shrub growing throughout India and commonly known as salparni. The active principal from Desmodium gangeticum glucosyl glycerolipid (pentadecanonicacid-3-(6-aminomethyl-3,4,5-trihydroxy-tetrahydro-pyran-2-ylxoy)-2-pentadecanoyl oxy propylester) and glycosphingolipid (cerebroside) exhibited in vitro antileishmanial and immunomodulatory activities, as it enhanced nitric oxide (NO) production and provided resistance against infection established in peritoneal macrophages by the protozoan parasite Leishmania donovani.

Echinacea

Echinacea is one of the most highly regarded immune supporting herbs available. Indigenous to North America, echinacea was traditionally used by Native Americans for a variety of ailments such as colds, coughs, sore throats, infections, and snake and insect bite bites. Several varieties of echinacea are available (e.g., Echinacea angustifolia, E. purpurea, E. pallida). Most seem to possess similar effects; however, some differences in chemistry have been noted. A number of clinical studies have demonstrated positive results in patients given echinacea to help boost immune function. Among its many immune modulating activities reported, activation of macrophages and secretion of lysosomal enzymes has been demonstrated most convincingly. However, novel mechanisms of action include effects on B and T lymphocytes as well as NK cells. In particular, Currier and Miller observed that upon incorporating Echinacea in the daily diet of elderly mice for only 14 days NK cell production in the bone marrow, as well as the number of mature functional NK cells reaching the spleen, increased to levels found in young adults. Recent research suggests that the high molecular weight polysaccharides present in echinacea have potent non-specific stimulatory actions on the immune system, specifically phagocytosis. Additionally, other components (e.g., echinacoside, chicoric acid) appear to have antibacterial and antiviral-like properties.

Eclipta alba

Eclipta alba (Family Asteraceae) grows in tropical and subtropical countries at an altitude of up to 2000 meters. In India, it is called “Bhringraj”. In traditional medicine, whole dried herb powder is used in liver disorders, especially jaundice. The herb contains wedelolactone and dimethyldelactone as coumestan derivatives and recently, a triterpenoidal saponin, “eclalbatin”, has also been isolated from this plant. E. alba, increased the phagocytic index and antibody titer significantly and the F ratios of the phagocytic index and WBC count are also significantly when it was tested using carbon clearance, antibody titer and cyclophosphamide immunosuppression parameters.

Emblisca officinalis

Emblisca officinalis (Phyllanthus emblica) commonly known as Amla belonging to family Euphorbiaceae. A simple aqueous extract of Emblisca officinalis (Phyllanthus emblica) fruit has shown to protect mice against the chromosome-damaging effects of the well known carcinogen 3, 4-benzo (a) pyrene (67). The protective effect against this type of damage therefore most likely involves the antioxidant activities of the P. emblica fruit extract. An anti-tumour effect of a P. emblica aqueous fruit extract was demonstrated in tumour-bearing mice, resulting in a 35% increase in life span (68). The anti-tumour activity was shown to be mediated primarily through enhanced natural killer cell activity and antibody-dependent cellular cytotoxicity. Another study showed an aqueous extract of P. emblica to significantly reduce induced solid tumors in mice in a manner suggesting interaction with cell cycle regulation (69). Extracts of P. emblica fruit inhibited the proliferation of four human tumour cell lines in vitro (70). Pyrogallol was identified as an active component of the extracts. Additionally, preliminary evidence suggests that Amla may help to boost immune response, presumably due to its vitamin C content (71). Vitamin C is believed to have an effect on the common cold primarily because of its role in the phagocytic function of leukocytes. Research suggests that supplemental vitamin C may help to enhance leukocyte activity and mobilization. Leukocytes contain very high concentrations of ascorbic acid that diminish with infection and return to normal after recovery. Vitamin C has been clearly linked to the modulation of immune function, particularly in the context of novel research showing improved cognitive status in patients with neurodegenerative disorders.

Fenugreek (Trigonella foenum- graecum)

Trigonella foenum-graeicum (family Leguminosae) is an annual herb widely grown in India, Egypt, and Middle Eastern countries. Fenugreek has also shown an overall stimulatory effect on the specific as well as non-specific immune functions in mice. The immunomodulatory effect of the extract was observed in mice treated orally with 50 and 100 mg/kg of the extract. At the stated dose, it increased the
bone marrow cell counts indicating its stimulatory effect on haematopoietic stem cells of bone marrow. It was most effective in inducing the immune functions at the dose of 100 mg/kg (77). Furthermore, the extract showed stimulatory effects on macrophage (the body's primary line of defense against infections). Macrophages play a role in cell mediated immunity by producing various kinds of cytokines like interleukin, interferon, tumor necrosis factor (TNF) and active substances like prostaglandin, hydrogen peroxide, super oxide and nitrite (77). Plant extract elicited a significant increase in phagocytic index and phagocytic capacity of macrophages. Stimulatory response of plant extract was also observed in lymphoproliferation assay but the response was weak.

Ginseng
Herbal remedies known as “ginseng” are based on the roots of several distinct species of plants, mainly Korean or Asian ginseng (Panax ginseng), Siberian ginseng (Eleutherococcus senticosus), and American ginseng (Panax quinquefolius). All of these species are in the Araliaceae plant family, but each has its own specific effects on the body. The main active agents in Panax ginseng are ginsenosides, which are triterpene saponins. The majority of published research on the medicinal activity of Panax ginseng has focused on ginsenosides (79). Ginseng is the other herbal that shows much promise as an immune modulating NHP. Indeed, it appears to have both immunostimulant and immunosuppressant activities, which would lend credence to the view that ginseng is an ‘adaptogenic’ NHP. Immunostimulant activities have been attributed to polysaccharide fractions, notably acting on both macrophages and B lymphocytes (80, 81). A study of 227 healthy volunteers demonstrated that daily administration of 100 mg of G115 for 12 weeks enhanced the efficacy of polyvalent influenza vaccine. The patients who received ginseng had a lower incidence of influenza and colds, higher antibody titers, and higher natural killer cell activity levels (82). Another study in 60 healthy volunteers showed enhanced chemotaxis, phagocytosis, increased total lymphocyte count, and increased numbers of T helper cells in those who received G115 in a dosage of 100 mg twice daily for eight weeks (83). In a study of 75 patients with acute exacerbation of chronic bronchitis that was treated with antibiotics or antibiotics plus ginseng, those in the ginseng group showed faster bacterial clearance (84).

Goldenseal
Goldenseal (Hydrastis canadensis), belonging to family Ranunculaceae also indigenous to North America, is commonly used in conjunction with echinacea for the treatment of colds and flu. Berberine is believed to have immune stimulating properties (85). Preliminary research suggests that berberine may help to increase macrophage activity, and it is also reported to increase blood supply to the spleen, which may help to facilitate the immune supporting activities of this organ (86, 87).

Janakia arayalpathra
Janakia arayalpathra Joseph & Chandras (Periplocaceae) is a perennial woody laticiferous shrub (88, 89). Recent pharmacological investigations of the root extract of the plant revealed immunomodulatory and anticancer properties. It stimulated an increase in humoral antibody titres and also of antibody secreting spleen cells in the plague forming cells assay following immunization with sheep erythrocytes. It also increased the number of peritoneal macrophages and produced an increase in delayed hypersensitivity reaction in mice (90).

Mangifera indica L.
Mangifera indica L. (Anacardiaceae) commonly known as Mango is claimed to possess numbers of therapeutic uses. Chattopadhyay et. al. have been reported in vitro immunomodulatory activity M. indica (91). Alcoholic extract of stem bark containing 2.6% of mangiferin had promising in vivo immuno-stimulatory effect. Further it was confirmed that immunostimulatory effect due to cell mediated and humoral antibody mediated activation of T and B cell. (92)

Mollugo verticillata
Mollugo verticillata L. (Molluginaceae) is an annual herb with prostrate growth habit. Ethanol extracts of M. verticillata could directly increase NO release by peritoneal cells, but suppress the immune response of these cells when treated with BCG antigen and Mycobacterium tuberculosis whole antigen (TB). From preliminary phytochemical test quercetin and triterpenoid glycosides were found in the ethanolic extract of M. verticillata, and those compounds are probably responsible for the effect of this plant material on the immune system (93).

Nigella sativa
Nigella sativa (Ranunculaceae) is commonly grows in Europe, Middle East, and Western Asia. As a natural remedy people take N. sativa seed or oil as a promoter of good health and for the prophylaxis of common cold and asthma. In view of that El-Kadi and Kandil (94) investigated reported that the administration of 1g twice daily in human volunteers enhanced immune functions as manifested by improved helper T cell (T4) to suppressor T cell (T8) ratio and an improved natural killer cell activity. However, there was a decrease in the immune globulin (IgA, IgG and IgM) levels. Moreover, Haq et al (95) noticed that N. sativa enhanced the production of interleukin-3 by human lymphocytes when cultured with pooled allogenic cells or without any added stimulator. In another study on mixed lymphocyte culture, it observed that whole N. sativa seeds and its purified proteins demonstrated stimulatory as well as suppressive effects depending upon the donor and the concentration used. Stimulant effect was observed with fractioned N. sativa proteins (P1 and P2) with a maximum effect at 10 µg/ml. Suppressive effect was observed with N. sativa seeds and high concentrations of all of its four proteins when lymphocytes were activated with poked-weed mitogen. In culture medium with non-activated peripheral blood mononuclear cells and with allogenic cells whole N. sativa produced large quantities of IL-1 beta, but no effect was seen on IL-4 secretion. The effect on IL-8 production was variable. However, a stimulatory effect of whole N. sativa and its fractionated proteins was noticed on the production of TNF in both non-activated and mitogen activated cells (96). The ethyl-acetate
chromatographic fraction of ethanolic extract of N. sativa has also been reported to potentiate cellular immune responses (97).

**Pleioblastus amarus**

*Pleioblastus amarus* (Gramineae) occurs widely in South China. The dried tender leaves of the plant are used in Chinese herbal medicine as antipyretic and diuretic agents (State Administration of Traditional Chinese Medicine, 1999). Flavones glucosides (1-3) has been isolated and found to be responsible for the in vitro immunomodulatory activity as compound 1 inhibited significantly (P<0.01) the proliferation of murine T cells and stimulated significantly (P<0.01) the proliferation of murine B lymphocytes in vitro, compound 2 and 3 stimulated significantly (P<0.01) the proliferation of murine B lymphocytes (98).

**Salicornia herbacea**

*Salicornia herbacea* has no leaves, but is formed of cylindrical branches of a light green color. It grows naturally in the western coast of Korean peninsula, especially in the salt marshes and on the muddy seashores. The immunomodulatory activities of extract were examined on a mouse monocytic cell line, RAW 264.7 cells and found that extract activated RAW cells to produce cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β, and nitric oxide (NO) dose dependently. Polysaccharides originated from *S. herbacea* possess potent immunomodulatory activity due to not only activate monocytes cells strongly, but also induce differentiation of monocytic cells into macrophages (99).

**Silybum marianum**

Blessed Milk Thistle (*Silybum marianum*) is a milk thistle, a plant of the Asteraceae family. *Silybum Marianum* is used for modulation of cytokine expression, which is important for immune responses. Cytokines are involved with regulation of phagocytes, immune defense cells, and other nonspecific body defenses. It contains flavonolignan Silymarin, which is an important bioactive principle having anticancer, antiinflammatory, antioxidant and immunomodulatory effects (100). Clinical studies conducted in Hungary also demonstrated silymarin to have immunomodulatory effects in liver disease (101, 102). Silymarin exerted no significant effects on un-stimulated polymorphonuclear (PMN) cell motility, phagocytic or chemotactic activities; however, when the PMNs were stimulated, silymarin inhibited myeloperoxidase release. Incubation of PMNs with silymarin prevented the action of the leukocyte motility inhibitor, FMLP (103, 104). Silymarin inhibited leukotriene production and had an antifibrotic effect (105). In healthy volunteers, silybin enhanced leukocyte motility (103). In a double blind, placebo-controlled trial of 40 patients with alcoholic cirrhosis, treatment with silymarin increased lectin-induced lymphoblast transformation, decreased the percentage of OKT8+ cells and suppressed lymphocytotoxicity significantly more than in the placebo treated group (106). Immunostimulatory effect of *Silybum marianum* (milk thistle) extract have also been investigated and found to be beneficial in increasing the immunity to infectious diseases (107).

*Tinospora Cordifolia*

Guduchi (*Tinospora cordifolia*) is a large, glabrous, deciduous climbing shrub belonging to the family menispermaceae. It is distributed throughout tropical Indian subcontinent and China, ascending to an altitude of 300m (108). *T. cordifolia* is reported to benefit the immune system in a variety of ways (109). The alcoholic and aqueous extracts of *T. cordifolia* have been tested successfully for immuno-modulatory activity (110). It helps increase the effectiveness of WBC and builds up the body’s immune system. TC-1 (clerodane furano diterpene glycoside), TC-2 (cordioside), TC-4 (syringin), TC-5 (cordifolioside A), TC, i5 (cordifolioside B) and TC-7 (cordiol) isolated from *Tinospora cordifolia* (111) are found to have anticomplement and immuno-stimulating activities. *Tinospora cordifolia* is reported for its various immunopharmacological activities, e.g. antioxidant properties and reducing toxic side effects of CP-induced toxicity, anticomplementary and immunomodulatory activities. Immunopotentiating effect is due to augmentation of IgG antibodies (112). Their effect was found to be dose dependent and at higher concentrations, antibody production was significantly increased (113).

**Viscum album** (*Mistletoe*)

The main immunostimulatory constituents of mistletoe are the glycosylated lectins, ML-I, ML-II and ML-III. The major component is ML-I (viscumin), a member of the type II ribosome-inactivating proteins, which is used to standardize mistletoe extracts. It consists of two polypeptide chains linked by a disulphide bridge. The A-chain has enzymatic RNA-cleaving activity and the B-chain binds to the target cell. ML-I has a broad range of affinities for α/β-linked galactopyranosyl residues. High nanogram concentrations of all three mistletoe lectins are cytotoxic. This action is due to ribosome inactivation by the RNA N-glycosidase A-chain (115), leading to induction of apoptosis, possibly through activation of cation channels. At lower concentrations, ML-I and ML-I-standardized mistletoe extracts stimulate release of IL-1, IL-6 and TNF-α from peripheral blood mononuclear and skin cells (116).

**Withania Somnifera**

*Withania somnifera*, commonly known as Indian ginseng, has been an important herb in the Ayurvedic and indigenous medical systems for over 3000 years. It is a small, woody shrub in the Solanaceae family. *Withania somnifera* has been revealed as an immunostimulator in immunosuppressed animal models (117) and also an immunoregulator in immune inflammation animal models (118). Administration of *Withania somnifera* extract was found to significantly reduce...
leucopenia induced by cyclophosphamide (CP) treatment, indicating *Withania somnifera* could reduce the CP-induced toxicity and its usefulness in cancer therapy (119). Methanolic extract of *Withania somnifera* exhibited radioprotective effect in normal BALB/c mice with increased bone marrow cellularity and reduction in chromosomal damage caused by sub lethal dose of gamma radiation (120). Enhanced levels of interferon (IFN)-gamma, IL-2, and granulocyte macrophage colony-stimulating factor (GM-CSF) in normal BALB/c mice were observed on administration of extract from roots of *Withania somnifera*. The lowered levels of IFN-gamma, IL-2, and GM-CSF after treatment with CP were reversed by administration of *W. somnifera* extract with lowered levels of TNF-alpha, indicating immunopotentiating and myeloprotective effect (121). *W. somnifera* extracts given intraperitoneal suppressed rat paw edema induced by carrageenan as well as in a granuloma pouch assay (122, 123). Withanolides inhibit murine spleen cell proliferation (124) and an extract of *W. somnifera* reversed ochratoxin's suppressive effect on murine macrophage chemotaxis (125). Withanolide glycosides activated murine macrophages, phagocytosis, and increased lysosomal enzymatic activity secreted by the macrophages, while also displaying anti-stress activity and positive effects on learning and memory in rats (126). The stimulation of macrophages was invoked to explain activity versus experimental aspergillosis in mice (127). The use of *W. somnifera* as a general tonic to increase energy and prevent disease may be partially related to its effect on the immune system. Glycowithanolides and a mixture of sitoindosides IX and X isolated from WS were evaluated for their immunomodulatory and central nervous system effects (antistress, memory, and learning) in Swiss mice (15-25 g, 5-6 months old) and Wistar strain albino rats (120-150 g and 250-300 g) (128).
### Table: 1 Some Other Immunomodulatory Plants

<table>
<thead>
<tr>
<th>Name</th>
<th>Family</th>
<th>Chemical Moiety</th>
<th>Plant Part</th>
<th>Pharmacological Activity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinidia macrosperma</td>
<td>Actinidiaceae</td>
<td>Alkaloids</td>
<td>Aqueous extract of plant</td>
<td>Immunostimulatory</td>
<td>129</td>
</tr>
<tr>
<td>Aloe vera</td>
<td>Aloaceae</td>
<td>Carn750</td>
<td>Leaves</td>
<td>Selectively stimulates cytokines, activates lymphocytes</td>
<td>130</td>
</tr>
<tr>
<td>Astragalus membranaceus</td>
<td>Leguminosae</td>
<td>Asparagine, calycosin, cycloastragenol</td>
<td>Roots</td>
<td>Increase macrophage count</td>
<td>131</td>
</tr>
<tr>
<td>Boswellia serrata</td>
<td>Burseraceae</td>
<td>Boswellic acid</td>
<td>bark</td>
<td>Anti-anaphylactic and mast cell stabilization</td>
<td>132</td>
</tr>
<tr>
<td>Boswellia carteri Birdwood</td>
<td>Burseraceae</td>
<td>Triterpenoids</td>
<td>bark</td>
<td>Immunostimulant action on T-lymphocytes</td>
<td>133</td>
</tr>
<tr>
<td>Cichorium intybus</td>
<td>Asteraceae</td>
<td>Sesquiterpenes</td>
<td>roots</td>
<td>complete inhibitory effect on the proliferation of lymphocytes in the presence of PHA (phytohemagglutinin)</td>
<td>134</td>
</tr>
<tr>
<td>Chlorophytum borivilianum</td>
<td>Liliaceae</td>
<td>Sapogenins</td>
<td>Roots</td>
<td>Immunostimulatory</td>
<td>135</td>
</tr>
<tr>
<td>Crinum latifolium</td>
<td>Amaryllidaceae</td>
<td>Ambelline and 1,2-beta-Epoxyambelline</td>
<td>Plant leaves</td>
<td>enhance neopterin production in unstimulated peripheral mononuclear cells, whereas an effective reduction of neopterin formation in cells stimulated with concanavalin A, phytohemagglutinin</td>
<td>136</td>
</tr>
<tr>
<td>Desmodium gangeticum</td>
<td>Leguminosae</td>
<td>cerebroside</td>
<td>Whole plant</td>
<td>Immunostimulatory</td>
<td>137</td>
</tr>
<tr>
<td>Euphorbia tirucalli Boiss</td>
<td>Euphorbiaceae</td>
<td>biopolymeric</td>
<td>Whole plant</td>
<td>suppression of CD4 and CD8 T cells, inhibition of intracellular Interleukin-2 and Interferon-gamma</td>
<td>138</td>
</tr>
<tr>
<td>Plant Name</td>
<td>Family</td>
<td>Chemical Compounds</td>
<td>Part of Plant</td>
<td>Activity</td>
<td>Page</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------</td>
<td>---------------------</td>
<td>---------------------</td>
<td>-----------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Ficus benghalensis</td>
<td>Moraceae</td>
<td>Phenolic compounds</td>
<td>Aerial roots</td>
<td>Immunostimulatory</td>
<td>139</td>
</tr>
<tr>
<td>Ganoderma lucidum</td>
<td>Ganodermataceae</td>
<td>glycoproteins</td>
<td>Fruiting bodies</td>
<td>Selectively stimulate cytokine</td>
<td>140</td>
</tr>
<tr>
<td>Orbignya phalerata</td>
<td>Areaceae</td>
<td>Bioactive polysaccharide</td>
<td>Mesocarp of fruits</td>
<td>Enhanced phagocytosis</td>
<td>141</td>
</tr>
<tr>
<td>Petieveria alliacea</td>
<td>Phytolaccaceae</td>
<td>dibenzyltrisulphide</td>
<td>Whole plant</td>
<td>Immunostimulant</td>
<td>142</td>
</tr>
<tr>
<td>Piper kadsura</td>
<td>Piperaceae</td>
<td>Futoquinol, galgravin, piperlactam, piperolactam</td>
<td>Stems</td>
<td>Suppression of human mononuclear cells (HMNC) proliferation</td>
<td>143</td>
</tr>
<tr>
<td>Piper longum</td>
<td>Piperaceae</td>
<td>Piperine</td>
<td>Alcoholic extract of the fruits</td>
<td>Increased the total WBC count</td>
<td>144</td>
</tr>
<tr>
<td>Scutellaria barbata</td>
<td>Lamiaceae</td>
<td>Apigenin</td>
<td>Roots</td>
<td>Toxic to MRSA</td>
<td>145</td>
</tr>
<tr>
<td>Scutellaria baicalensis</td>
<td>Lamiaceae</td>
<td>Wogonin</td>
<td>Roots</td>
<td>Stimulates TNF-, activates iNOS</td>
<td>146</td>
</tr>
<tr>
<td>Zingiber officinale</td>
<td>Zingiberaceae</td>
<td>Gingerols</td>
<td>Rhizome</td>
<td>Potent B cell stimulant</td>
<td>147</td>
</tr>
</tbody>
</table>
CONCLUSION

Due to economic constraints, providing modern medicinal healthcare in developing countries such as India is still a far-reaching goal. The most commonly used drugs of modern medicine such as aspirin, anti-malarials, anti-cancers, digitals, etc. have originated from plant sources. Out of an estimated 2,50,000 higher plants, less than 1% have been screened pharmacologically and very few in regard to immunomodulatory. Therefore, it is prudent to look for options in herbal medicine as immunomodulatory as well. We have been working continuously towards establishing the scientific basis of use of certain plants in immune disease. Such an ethnomedicinal approach for disease is a practical, cost-effective and a logical for its treatment. The goals of medicine no matter to which group it belongs, are the same i.e. the welfare of the patient. One can look towards a future medicine no matter to which group it belongs, are the same scientific basis of use of certain plants in immune disease. 

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259


