Pharmacognosy Reviews
Vol 1, Issue 2, Jul-Dec, 2007

PHCOG REV.
An official Publication of Phcog.Net

Phcog Rev.: Review Article
Immunomodulatory Plants: A Phytopharmacological Review

Hemant sagrawat[1]and Md. Yaseen Khan[2]

[1]*Research Associate, Getz Pharma Research Pvt. Ltd., Mumbai*

[2]*Department of Phytopharmaceuticals and Natural Products, Institute of Pharmacy, Nirma University of Science and Technology, S.G. highway, Ahmedabad- 382 481.*

**Author for correspondence: E-mail: hemantsagrawat@gmail.com, mohammadyaseenkhan@gmail.com*

Phone: +91-9819675295, 9904044934

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 clinincal 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 has 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 neoandrographolide. 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 immunse 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.

Asparagus racemosus

Immunomodulating property of *Asparagus racemous* (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 of adhesions 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-I (IL-I) and tumor necrosis factor a (TNF-α) 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 lmmunomodulatory 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).

Boerrhiva diffusa

Boerhaavia diffusa Linn. (Nyctaginaceae) 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 *Boerrhiva diffusa* significantly restored the suppressed humoral response in stressed rats wherein *Boerrhiva 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 (Apiaceae) 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 powder of *C. asiatica* have been reported (32). Asiaticoside is the major constituents of *C.asiatica* (33).

Clausena excavate

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 $C_{21}H_{20}O_6$, 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-

dione) and its chemical structure (41) is depicted in Fig. Curcumin has been found to modulate the growth and cellular response of various cell types of the immune system. 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 ((42) 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 (43). 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 (44). In still another report, curcumin inhibited the activation of human V *γ δ*T cells induced by phosphoantigens (45). **Effect on *B cells*** Inhibits Epstein bar virus-induced B-cell proliferation and immortaliztion (46). Increases B-cell proliferation in intestinal mucosa of mice (47). **Effect on *Macrophages*** Increases phagocytosis of macrophages and differentially regulates splenocyte proliferation (48). Reduces the ROS generation ability of macrophages and secretion of lysosomal enzymes (49, 50). Differentially activates macrophages by down regulating Th1 and NO production (51).

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 (pentadecanoicacid-3-(6-aminomethyl-3,4,5-trihydroxy-tetrahydro-pyran-2-yloxy)-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* (52-54).

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 properties; however, some differences in chemistry have been noted (55). A number of clinical studies have demonstrated positive results in patients given echinacea to help boost immune function (56-58). Among its many immune modulating activities reported, activation of macrophages has been demonstrated most convincingly. However, novel mechanisms of action include effects on B and T lymphocytes as well as NK cells (59, 60). 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 (59, 61). Recent research suggests that the high molecular weight polysaccharides present in echinacea have potent non-specific stimulatory actions on the immune system, specifically phagocytosis (62, 63). Additionally, other components (e.g., echinacoside, chicoric acid) appear to have antibacterial and antiviral-like properties (64).

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 (65). The herb contains wedelolactone and dimethylwedelolactone as coumestan derivatives and recently, a triterpenoidal saponin, "eclalbatin", has also been isolated from this plant (66). *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.

Emblica officinalis

Emblica officinalis (*Phyllanthus emblica)* commonly known as Amla belonging to family Euphorbiaceae. A simple aqueous extract of *Emblica 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 meditated 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 (72-74). 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 (75).

Fenugreek (Trigonella foenum- graecum)

Trigonella foenum-graecum (family Leguminosea) is an annual herb widely grown in India, Egypt, and Middle Eastern countries (76). 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 senticosu*), 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 plaque 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 posses number 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 fractionated *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 potenciate 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 and3 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 mashes 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)-1ß, and nitric oxide (NO) dose dependently. Polysaccharides originated from *S. herbacea* possess potent immunomodulatory activity due to not only activate monocytic 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). Syringin (TC-4) and cordial (TC-7) inhibited the *in vitro* immunohaemolysis of antibody coated sheep erythrocytes by guinea pig serum. The reduced immunohaemolysis was found to be due of inhibition of the C3-convertase of the classical complement pathway. The compounds also gave rise to a significant increase in IgG antibodies in serum. Humoral and cell-mediated immunity were also dose-dependently enhanced. Macrophage activation was reported for cordioside (TC-2), cordiofolioside A (TC-5) and cordiol (TC-7) and this activation was more pronounced with increasing incubation times (114).

***Viscum album* (Mistletoe)**

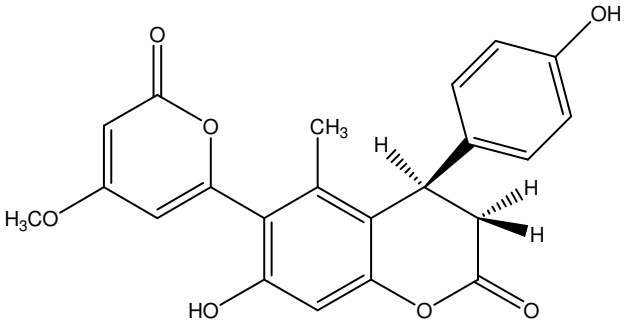
The main immunostimulatory constituents of mistletoe are the glycosylated lectins, ML-I, ML-II and ML-III. The major component is ML-I (viscumin), a member of the type II ribosome-inactivating proteins, which is used to standardize mistletoe extracts. It consists of two polypeptide chains linked by a disulphide bridge. The A-chain has enzymatic rRNA-cleaving activity and the B-chain binds to the target cell. ML-I has a broad range of affinities for α/ß-linked galactopyranosyl residues. High nanogram concentrations of all three mistletoe lectins are cytotoxic. This action is due to ribosome inactivation by the rRNA 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 Sominifera

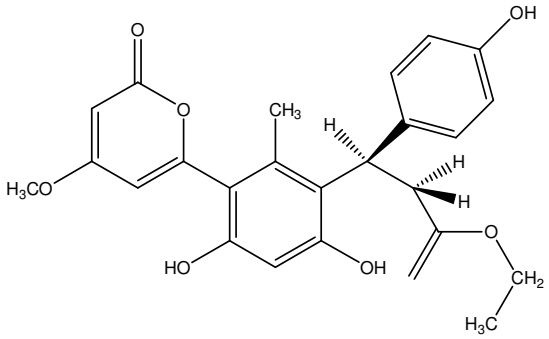
Withania somnifera, commonly known as Indian ginseng, has been an important herb in the Ayurvedic and indigenous medical systems for over 3000 years. It is a small, woody shrub in the Solanaceae family. *Withania somnifera* has been revealed as an immunostimulator in immunosuppressed animal models (117) 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).

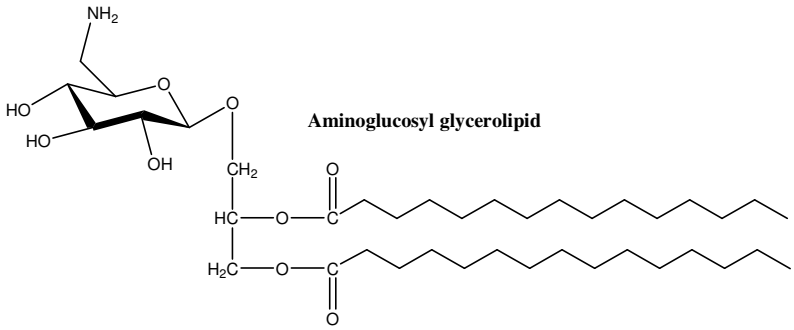
Structure Of Immunomodulatory Phytoconstituents From Plants



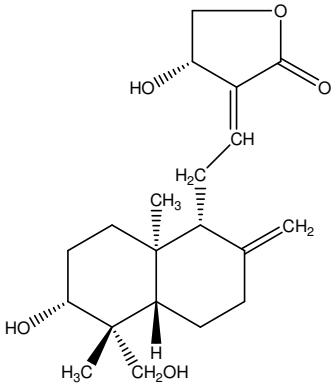
Aleo Compund 1



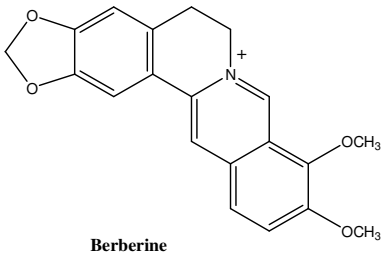
Aloe Compund 2



Aminoglucosyl glycerolipid

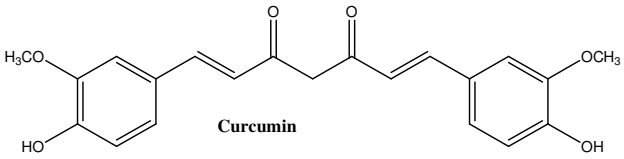


Andrographolide

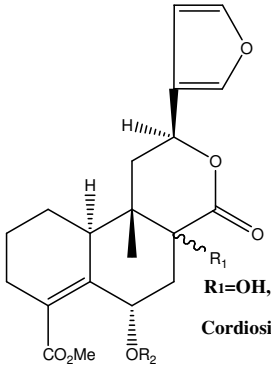


Berberine

PHCOG REV.
An official Publication of Phcog.Net

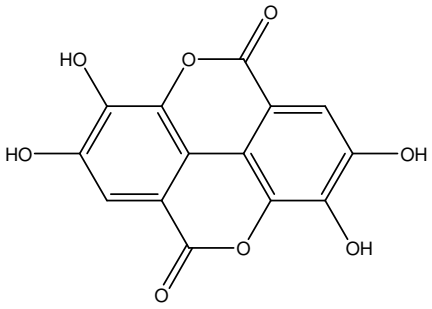


Curcumin

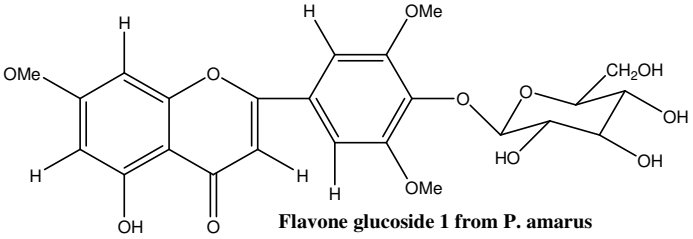


R1=OH, R2= D - glucopyranosyl

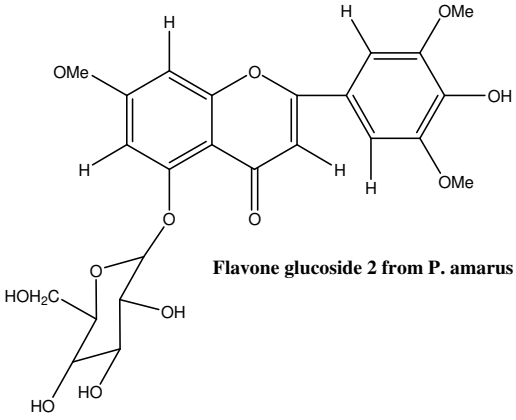
Cordioside



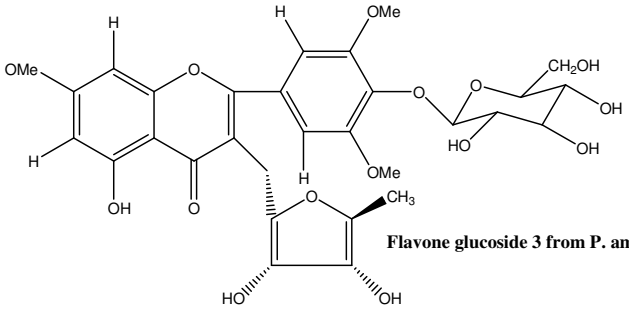
Ellagic acid



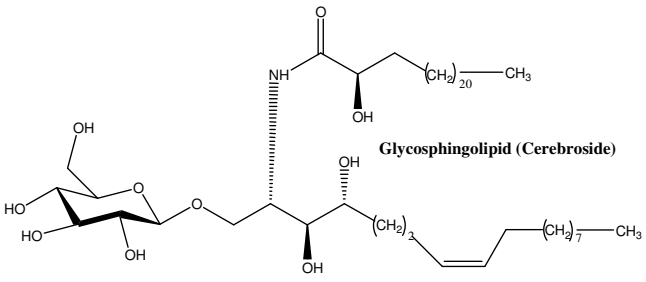
Flavone glucoside 1 from P. amarus



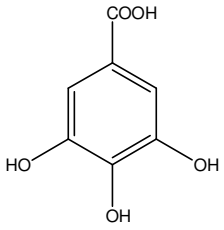
Flavone glucoside 2 from P. amarus



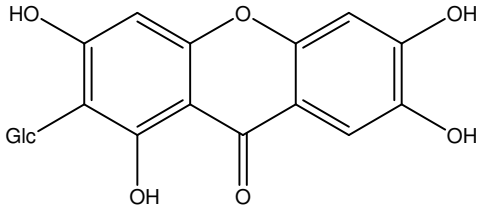
Flavone glucoside 3 from P. amarus



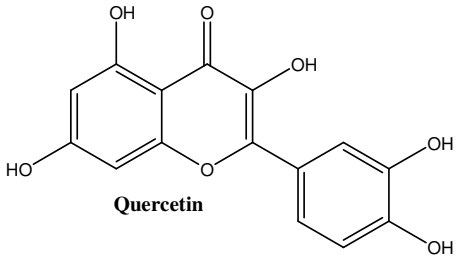
Glycosphingolipid (Cerebroside)



Gallic acid

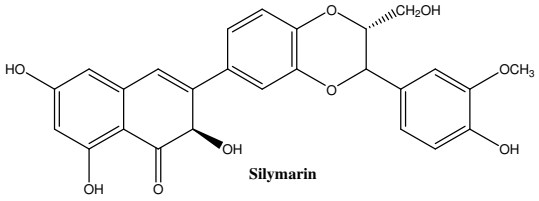


Mangiferin

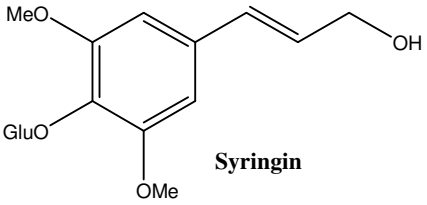


Quercetin

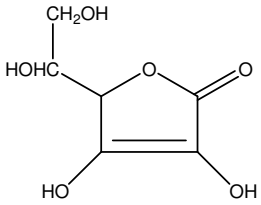
PHCOG REV.
An official Publication of Phcog.Net



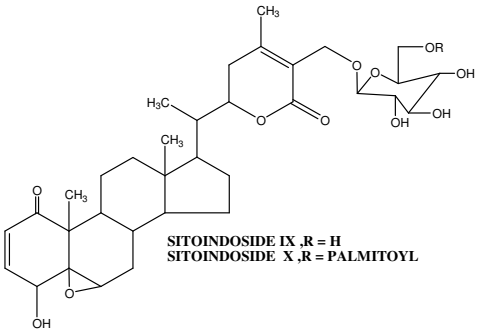
Silymarin



Syringin



Vitamin C



SITOINDOSIDE IX ,R = H
SITOINDOSIDE X ,R = PALMITOYL

PHCOG REV.
An official Publication of Phcog.Net

Table: 1 Some Other Immunomodulatory Plants

Name	Family	Chemical Moiety	Plant Part	Pharmacological Activity	Reference
Actinidia macrosperma	Actinidiaceae	Alkaloids	Aqueous extract of plant	Immunostimulatory	129
Aloe vera	Aloaceae	Carn750	Leaves	Selectively stimulates cytokines, activates lymphocytes	130
Astragalus membranaceus	Leguminosae	Asparagine, calycosin, cycloastragenol	Roots	Increase macrophage count	131
Boswellia serrata	Burseraceae	Boswellic acid	bark	Anti-anaphylactic and mast cell stabilization	132
Boswellia carteri Birdwood	Burseraceae	Triterpenoids	bark	Immunostimulant action on T-lymphocytes	133
Cichorium intybus	Asteraceae	Sesqueterpenes	roots	complete inhibitory effect on the proliferation of lymphocytes in the presence of PHA (phytohemagglutinin)	134
Chlorophytum borivilianum	Liliaceae	Sapogenins	Roots	Immunostimulatory	135
Crinum latifolium	Amaryllidaceae	Ambelline and 1,2-beta-Epoxyambelline	Plant leaves	enhance neopterin production in unstimulated peripheral mononuclear cells, whereas an effective reduction of neopterin formation in cells stimulated with concanavalin A, phytohemagglutinin	136
Desmodium gangeticum	Leguminosae	cerebroside	Whole plant	Immunostimulatory	137
Euphorbia tirucalli Boiss	Euphorbiaceae	biopolymeric	Whole plant	suppression of CD4 and CD8 T cells, inhibition of intracellular Interleukin-2 and Interferon-gamma	138

Ficus benghalensis	Moraceae	Phenolic compounds	Aerial roots	Immunostimulatory	139
Ganoderma lucidum	Ganodermataceae	glycoproteins	Fruiting bodies	Selectively stimulate cytokine	140
Orbignya phalerata	Arecaceae	bioactive polysaccharide MP1.	Mesocarp of fruits	Enhanced phagocytosis	141
Petieveria alliacea	Phytolaccaceae	dibenzyltrisulphide	Whole plant	Immunostimulant	142
Piper kadsura	Piperaceae	futoquinol, galgravin, piperlactam S, piperolactam	stems	Suppression of human mononuclear cells (HMNC) proliferation	143
Piper longum	Piperaceae	Piperine	Alcoholic extract of the fruits	increased the total WBC count	144
Scutellaria barbata	Lamiaceae	Apigenin	Roots	Toxic to MRSA	145
Scutellaria baicalensis	Lamiaceae	Wogonin	Roots	Stimulates TNF-, activates iNOS	146
Zingiber officinale	Zingiberaceae	gingerols	Rhizome	potent B cell stimulant	147

CONCLUSION

Due to economic constraints, providing modern medical 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, digitalis, 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 ethnomedical 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 of integrated medicine and hope that research in alternative medicine will help identify what is safe and effective rather than marginalizing, unorthodox medical claims and findings.

REFERENCES

1. K. B. Flemming, *Reticuloendothelial System: A Comprehensive Treatise,* Vol. 8, New York (1985), pp. 247-284.
2. S. H. Kowalozyk-Bronisz and I. Paegelow. *Allerg. Immunol*. **32(1):** 57-64 (1986).
3. L. D. Smirnov and V. S. Suskova, *Khim.-farm. Zh.,* **7:** 773-784 (1989).
4. B. Patwardhan, D. Kalbag, P. S. Patki and B. A. Nagsampagi. Search of immunomodulatory agents: a review. *Indian Drugs* **28(2):** 348–358(1990).
5. R. B. Diasio and A. F. LoBuglio: *Immunomodulators: Immunosuppressive agents and immunostimulants*. Goodman and Gilman's, The Pharmacological Basis of Therapeutics, McGraw-Hill, NewYork, **9:** 1291–1307(1996).
6. C. K. Atal, M. L. Sharma, A. Kaul and A. Khajuria. Immunomodulating agents of plant origin I, Preliminary screening. *Journal of Ethnopharmacology* **18:** 133–141(1986).
7. X. F. Zhang, H. M. Wang, Y. L. Song, L. H. Nie , L. F. Wang , B. Liu, P. P. Shen and Y. Liu. Isolation, structure elucidation, antioxidative and immunomodulatory properties of two novel dihydrocoumarins from *Aloe vera*. *Bioorg. Med. Chem Lett.* **16(4):** 949-53(2006).
8. J. A. Duke. Handbook of biologically active phytochemicals and their activities. CRC Press: *Boca Raton*, (1992).
9. A. Puri, R. Saxena, R. P. Saxena and K. C. Saxena. Immunostimulant agents from *Andrographis paniculata*. *J. Natural Products*, **56(7):** 995-99(1993).
10. V. Melchior, et al. Controlled clinical study of standardized *Andrographis paniculata* extract in common cold - a pilot trial. *Phyotmed*. **3:** 315-8(1996).
11. T. Matsuda, M. Kuroyanagi, S. Sugiyama, K. Umehara, A. Ueno and K. Nishi. Cell differentiation-inducing diterpenes from *Andrographis paniculata*. Nees. *Chem. Pharm.* Bull (Tokyo) **42(6):** 1216-25(1994).
12. P. B. Talukdar and S. Banerjee. Studies on the stability of andrographolide. *Indian J.Chem,* **6:** 252-54(1968).
13. S. Dahanukar, U. Thatte, N. Pai, P.B. Mose and S. M. Karandikar. Protective effect of *Asparagus racemosus* against induced abdominal sepsis. *Indian* Drugs. **24:** 125-8(1986).
14. U. Thatte, S. Chhabria, S. M. Karandikar and S. Dahanukar, Immunotherapeutic modification of E. coli induced abdominal sepsis and mortality in mice by Indian medicinal plants. *Indian Drugs*. **25:** 95-7(1987).
15. N. N. Regh, H. M. Nazareth, A. Isaac, S. M. Karandikar, S. A. Dahanukar. Immunotherapeutic modulation of intraperitoneal adhesions by *Asparagus racemosus*. *J Postgrad Med*. **35:** 199-203(1989).
16. J. N. Dhuley. Effect of some Indian herbs on macrophage functions in ochratoxin a treated mice. *J Ethnopharmacol*. **58:** 15-20(1997).
17. S. Muruganadan, H. Garg, J. Lal, S. Chandra and D. Kumar. Studies on the immunostimulant and antihepatotoxic activities of *Asparagus racemosus* root extract. *J Med. Arom. PI Sci*. **22:** 49-52(2000).
18. J. M. Vander Nat, J. P. A. M. Kierx, H. Van Dijk, K. T. D. De Silva and R. P. Labadie, Biological activities and medicinal properties of neem (*Azadirachta indica*) *J. Ethnopharmacol.* **19:** 125–131(1987).
19. S. M. Njiro and M. W. Kafi-Tsekpo, Effect of an aqueous extract of Azadirachta indica on the. immune response in mice. *Ondersterpoort J.Vet. Res*. **66:** 59–62(1999).
20. P. Sen, P. K. Medinata, and A. Ray, Effects of *Azadirachta indica*_a Juss on some biochemical, immunological and visceral parameters in normal and stressed rats. *Indian J. Exp. Biol*., 1992, **12**, 1170–1175.
21. A. Ray, B. D. Banerjee, P. Sen, Modulation of humoral and cell mediated immune responses by *Azadirachta indica* in mice *ibid*, 34:698–701(1996).
22. S. N. Upadhyay, S. Dhawan, S. Garg and G. P. Talwar. Immunomodulatory effects of Neem (*Azadirachta indica*) oil. *Int. J. Immunopharmacol.* **14:** 1187–1193(1992).
23. G.P. Talwar, P. R. Vanshi, R. Misra, S. Mukherjee and S. Shah. Plant immunomodulators for termination of unwanted pregnancy and for contraception and reproductive health. *Immunology and Cell Biology*. **75:**190–192 (1997)
24. M. Sai Ram, S. K. Sharma, G. Ilavazhagan, Devendra Kumar and W. Selvamurthy. Immunomodulatory effects of NIM-76, a volatile fraction from Neem oil, *Journal of Ethnopharmacology*. **55:** 33-39(1997).
25. S. Mehrotra, K. P. Mishra, R. Maurya, R. C. Srimal and V. K. Singh. Immunomodulation by ethanolic extract of *Boerhaavia diffusa* roots. *Int Immunopharmacol*, **2:** 987-996(2002).
26. S. Mehrotra, V. K. Singh, S. S. Agarwal, R. Maurya and R. C. Srimal, Antilymphoproliferative activity of ethanolic extract of *Boerhaavia diffusa* roots. *Exptl Mol Pathol*, **72:** 236-242(2002).
27. A. A. Mungantiwar, A. M. Nair, U. A. Shinde, et al. Effect of stress on plasma adrenal cortisol levels and immune responsiveness in rats: modulation by alkaloidal fraction of *Boerhaavia diffusa. Fitoterapia,* **68:** 498-500(1997).
28. E. Zvetkova, B. Wirleitner, N. T. Tram, H. Schennach and D. Fuchs. Aqueous extracts of *Crinum latifolium* (L.) and *Camellia sinensis* show immunomodulatory properties in human peripheral blood mononuclear cells. *Int Immunopharmacol* **1:** 2143–2150(2001).
29. Kartnig T. Herbs, spices and medicinal plants- resent advances in Botany, Horticulture and Pharmacology Oryx press, Phoenix 3rd edi. 145–173(1988)
30. R.N. Chopra, S.L. Nayar, I.C. Chopra, Glossary of Indian Medicinal Plants, (Council of Industrial and Scientific Research, New Delhi, 1958) pp. 353.
31. J. DiCarlo, L. J. Haynes, N. J. Sliver and G. H. Phillips. Reticuloendothelial system stimulants of botanical origin. *J Reticuloendothelial Soc* **1:** 224–232(1964)
32. J. S. Patil, B. G. Nagavi, M. Ramesh, G. S. Vijayakumar. A study on the Immunostimulant activity of *Centella asiatica* in rats. *Ind Drugs* **38:** 711–714(1998).
33. M. G. Jayathirtha and S. H. Mishra Preliminary immunomodulatory activities of methanol extracts of *Eclipta alba* and *Centella asiatica*. *Phytomedicine* **11:** 361–365, 2004
34. L. M. Perry. Medicinal plants of East and South East Asia: attributed properties and used. Cambridge: *TheMITPress*,(1980).
35. T. S. Wu, S. C. Huang, P. L. Wu and C. S. Kuoh. Alkaloidal and other constituents from the root bark of Clausena excavate. *Phytochemistry,* **52:** 523(1999).
36. I. Chihiro, I. Masataka, K. Shinya, O. Mitsuo, T. Harukuni, N. Hoyoku and F. Hirochi. Chemical constituents of *Clausena excavata*: Isolation and structure elucidation of novel furanone-coumarins with inhibitory effects for tumor-promotion. *J Natl* Prod. **63:**1218(2000).
37. P. L. Rudi. Immunomodulatory compounds. Bioactive natural products: detection, isolation, and structure determination. London: *CRCPress*, (1993).
38. A. Manosroi, A. Saraphanchotiwitthaya and J. Manosroi. Immunomodulatory activities of *Clausena excavate*, Burm.f. wood extracts. *Journal of Ethnopharmacology* **89:** 155–160(2003).
39. A Leung: Encyclopedia of Common Natural Ingredients Used in Food, Drugs, and Cosmetics. New York, Wiley, 1980, pp 313– 314
40. V. Lampe, J. Milobedeska and V. Kostanecki. *Ber Dtsch Chem Ges* **43:** 2163, (1910).
41. V. Lampe and J. Milobedeska, *Ber Dtsch Chem Ges* **46:** 2235, (1913).
42. D. Ranjan, C. Chen, T. D. Johnston, H. Jeon and M. Nagabhushan. Curcumin inhibits mitogen stimulated lymphocyte proliferation, NF- κB activation, and IL-2 signaling. *J Surg Res* **121(2):** 171–177, (2004).
43. D. Ranjan, C. Chen, T. D. Johnston, H. Jeon and M. Nagabhushan. Curcumin blocks cyclosporine A-resistant CD28 costimulatory pathway of human T-cell proliferation. *J Surg Res* **77(2):** 174–178, (1998).
44. V. S. Yadav, K. P. Mishra, D. P. Singh, S. Mehrotra and V. K. Singh: Immunomodulatory effects of curcumin. *Immunopharmacol Immunotoxicol* **27:** 485–497, (2005)
45. B. Cipriani, G. Borsellino, H. Knowles, D. Tramonti, F. Cavaliere, G. Bernardi, L. Battistini and C. F. Brosnan. Curcumin inhibits activation of Vγ 9Vδ2 T cells by phosphoantigens and induces apoptosis involving apoptosis-inducing factor and large scale DNA fragmentation. *J Immunol* **167(6):** 3454–3462 (2001).
46. D. Ranjan, A. Siquijor, T. D. Johnston, G. Wu and M. Nagabhuskahn. The effect of curcumin on human B-cell immortalization by Epstein- Barr virus. *Am Surg* **64(1):** 47–51(1998).
47. M. Churchill, A. Chadburn, R. T. Bilinski, M. M. Bertagnolli. Inhibition of intestinal tumors by curcumin is associated with changes in the intestinal immune cell profile. *J Surg Res* **89:** 169–175(2000).
48. X. Li and X. Liu. Effect of curcumin on immune function of mice. *J Huazhong Univ Sci Technol Med Sci* **25(2):**137–140(2005).
49. B. Joe and B. R. Lokesh. Role of capsaicin, curcumin and dietary *n* – 3 fatty acids in lowering the generation of reactive oxygen species in rat peritoneal macrophages. *Biochim Biophys Acta* **1224(2):** 255– 263(1994)
50. B. Joe and B. R. Lokesh. Dietary *n* – 3 fatty acids, curcumin and capsaicin lower the release of lysosomal enzymes and eicosanoids in rat peritoneal macrophages. *Mol Cell Biochem* **203(1–2):** 153–161(2000).

51. S. Bhaumik, M. D. Jyothi and A. Khar. Differential modulation of nitric oxide production by curcumin in host macrophages and NK cells. *FEBS Lett* **483:** 78–82(2000).
52. E. Hardegger, G. Zanetti and K. Steiner. *Helv.Chim.Acta*, **46:** 282(1963).
53. F. Cateni, J. Zilic, G. Falsone, F. Hollan, F. Frausin and V. Scarcia. Preliminary biological assay on cerebroside mixture from Euphorbia nicaeensis All. Isolation and structure determination of five glucocerebrosides. *II Farmaco*, **58(9):** 809(2003).
54. P. K. Mishra, N. Singh, G. Ahmad, A. Dube and R. Maurya. Glycolipids and other constituents from Desmodium gangeticum with antileishmanial and immunomodulatory activities, *Bioorganic & Medicinal Chemistry Letters* **15:** 4543–4546 (2005).
55. J. M. Snow. *Echinacea (Moench) spp.* Asteraceae. *Protocol J Botan Med,* **2:** 18-24(1997).
56. B. Braunig, M. Dorn, E. Limburg, E. Knick, et al. *Echinacea purpurea* radix for strengthening the immune response in flu-like infections. *Ze itschrift Fur Phytotherapy,* **13:** 7-13(1992).
57. D. Schoneberger. The influence of immune-stimulating effects of pressed juice from *Echinacea purpurea* on the course and severity of colds. *Forum Immunology.* **8:** 2-12(1992).
58. C. Lersch, et al. Nonspecific immunostimulation with low doses of cyclophosphamide (LDCY) thymostimulin, and *Echinacea purpurea* extracts (echinacin) in patients with far advanced colorectal cancers: preliminary results. *Can Inves,* **10:** 343-8(1992).
59. N. L. Currier and S. C. Miller. Natural killer cells from aging mice treated with extracts from *Echinacea purpurea* are quantitatively and functionally rejuvenated *Exp Gerontol*, **35:** 627–39(2000).
60. N. L. Currier and S. C. Miller. *Echinacea purpurea* and melatonin augment natural-killer cells in leukemic mice and prolong life span. *J Altern Complement Med*, **7:** 241–51(2001).
61. L. Z-Y Sun, N. L. Currier and S. C. Miller. The American coneflower: a prophylactic role involving nonspecific immunity. *J Altern Complement Med*, **5:** 437–46(1999).
62. J. Roesler, et al. Application of purified polysaccharides from cell cultures of the plant *Echinacea purpurea* to test subjects mediates activation of the phagocyte system. *Int J Immunopharmacol*, **13:** 931-41(1991).
63. J. Roesler, et al. Application of purified polysaccharides from cell cultures of the plant *Echinacea purpurea* to mice mediates protection against systemic infections with Listeria monocytogenes and Candida albicans. *Int J Immunopharmacol*, **13:** 27-37(1991).
64. M. Wichtl, *Herbal Drugs and Phyotpharmaceuticals.* CRC Press: *Boca Raton*, (1994).
65. R.N. Chopra, S.L. Nayar, I.C. Chopra, Glossary of Indian Medicinal Plants, (Council of Industrial and Scientific Research, New Delhi, 1966) pp. 104.
66. R. K. Upadhyay, M. B. Pandey, R. N. Jha and V. B. Pandey. Eclalbatin, a triterpene saponin from *E. alba*. *Asian Nat Prod Res* **3:** 213–217 (2001).
67. P. Nandi, G. Talukder and A. Sharma. Dietary chemoprevention of clastogenic effects of 3, 4-benzo (a) pyrene by Emblica officinalis Gaertn. fruit extract. *British Journal of Cancer*. **76:** 1279-1283(1997).
68. K. Suresh, D. M. Vasudevan. Augmentation of murine natural killer cell and antibody dependent cellular cytotoxicity activities by *Phyllanthus emblica*, a new immunomodulator. *Journal of Ethnopharmacology*, **4:** 55-60(1994).
69. J. K. Jose, G. Kuttan, R. Kuttan. Antitumour activity of *Emblica officinalis. Journal of Ethnopharmacology*, **75:** 65-69(2001).
70. M. T. H. Khan, et al. Identification of pyrogallol as an antiproliferative compound present in extracts from the medicinal plant *Emblica officinalis*: Effects on in vitro cell growth of human tumor cell lines. *International Journal of Oncology*, **21:** 187-192(2002).
71. K. Suresh and D. M. Vasudevan. Augmentation of murine natural killer cell and antibody dependent cellular cytotoxicity activities by *Phyllanthus emblica*, a new immunomoldulator. *J Ethnopharmacol*. **44:** 55-60(1994).
72. M. Linder. Nutritional Biochemistry and Metabolism with Clinical Applications. 2nd ed. *Appleton & Lange*: Norwalk, CT. (1991).
73. G. Heuser and A. Vojdani. Enhancement of natural killer cell activity and T and B cell function by buffered vitamin C in patients exposed to toxic chemicals: the role of protein kinase-C. *Immunopharm Immunotox*. **19:** 291-312(1997).
74. A. Vojdani and M. Ghoneum. In vivo effect of ascorbic acid on enhancement of human natural killer cell activity. *Nutr Res*. **13:** 753-64(1993).
75. A. Martin. Antioxidant vitamins E and C and risk of Alzheimer's disease. *Nutr Rev*, **61:** 69–73(2003).
76. F. J. A. guilara, R. R. Ramos, S. P. Gutierrez, A. A. Contreras, C. C. Contreras-Weber and J. L. Flores-Saenz. Study of the anti-hyperglycemic effects of plants used as antidiabetics. *J. Ethnopharmacol.* **61:** 101–110(1998).
77. B. Bin-Hafeez, R. Haque, S. Parvez, S. Pandey, I. Sayeed and S. Raisuddin . Immunomodulatory effects of fenugreek (*Trigonella foenum graecum L.*) extract in mice. *Int Immunopharmacol*. **3(2):** 257-65(2003).
78. N. E. Kaminski, J. F. Roberts and F. E. Guthrie. A rapid spectrophotometric method for assessing macrophage phagocytic activity. *Immunology Letters*. **10:** 329-331(1985).
79. World Health Organization. WHO monographs on selected medicinal plants. Geneva: World Health Organization, (1999).
80. M. Wang, L. J. Guilbert, L. Ling, J. Li, Y. Wu, S. Xu, et al. Immunomodulating activity of CVT-E002, a proprietary extract from North American ginseng (*Panax quinquefolium*) *J Pharm Pharmacol*. **53:** 1515–23(2001).
81. V. A. Assinewe, J. T. Amason, A. Aubry, J. Mullin and I. Lemaire. Extractable polysaccharides of *Panax quinquefolius* L. (North American ginseng) root stimulate TNF alpha production by alveolar macrophages. *Phytomedicine*, **9:** 398–404(2002).
82. F. Scaglione, G. Cattaneo, M. Alessandria and R. Cogo. Efficacy and safety of the standardized *Ginseng* extract G115 for potentiating vaccination against the influenza syndrome and protection against the common cold [corrected]. *Drugs Exp Clin Res*. **22:** 65-72(1996).
83. F. Scaglione, F. Ferrara, S. Dugnani, M. Falchi, G. Santoro and F. Fraschini. Immunomodulatory effects of two extracts of *Panax ginseng* C.A. Meyer. *Drugs Exp Clin Res*. **16:** 537-42(1990).
84. F. Scaglione, K. Weiser and M. Alessandria. Effects of the standardized ginseng extract G115® in patients with chronic bronchitis: a nonblinded, randomised, comparative pilot study. *Clin Drug Invest*. **21:**41-5(2001).
85. J. E. Pizzorno and M. T. Murray. A Textbook of Natural Medicine. Vol. 1, Bastyr University Publications: *Seattle*, (1989).
86. J. A. Duke. The Green Pharmacy. Rodale Press: *Emmaus*, PA, (1996).
87. Y. Kumazawa, et al. Activation of peritoneal macrophages by berberine- type alkaloids in terms of induction of cytostatic activity. *Int J Immunopharmacol*. **6:** 587-92(1984).
88. J. Joseph and V. Chandrasekharan. *Bot. Soc.* **57:** 308–312(1978).
89. H. J. T. Venter and R. L. Verhoveven, *Taxon*, **46:**705–720(1997).
90. A. Subramoniam, S. Rajasekhran, P. G. Latha, D. A. Evans and P. Pushpangadan, *Fitoterapia*, **68:** 140–144(1996).
91. U. Chattopadhyay, L. Chaudhari and S. Ghosal. Immunostimulatory activity of mangiferin, a naturally occurring xanthone-C-glucoside. *Pharmaceutical Research* **3(5):** 307–308(1986).
92. N. Makare, S. Bodhankar and V Rangari. Immunomodulatory activity of alcoholic extract of *Mangifera indica L.* in mice *Journal of Ethnopharmacology*. **78:** 133–137(2001).
93. A. P. Ferreira1, G. L. G. Soares, C. A. Salgado, L. S. Gonçalves , F. M.Teixeira, H. C. Teixeira and M. A. C. Kaplan. Immunomodulatory activity of *Mollugo verticillata* L. Phytomedicine. **10:** 154–158, 2003
94. A. El-Kadi and O. Kandil. Effect of *Nigella sativa* (the black seed) on immunity. Proceeding of the 4th International Conference on Islamic Medicine, Kuwait. *Bull Islamic Med*. **4:** 344-8(1986).
95. A. Haq, M. Abdullatif, P. I. Lobo, K. S. Khabar, K. V. Sheth and S. T. Al-Sedairy. *Nigella sativa*: Effect on human lympocytes and polymorphonuclear leucocyte phagocytic activity. *Immunopharmacology*, **30 (2):**147-50(1995).
96. A. Haq, P. L. Lobo, M. Al-Tufail, N. R. Rama and S. T. Al-Sedairy. Immunomodulatory effect of *Nigella sativa* proteins fractionated by ion exchange chromatography. *Int J Immunopharmacol*, **2 (4):** 283-5(1999).
97. S. M. Swamy and B. K. Tan. Cytotoxic and imunopotentiating effects of ethanolic extract of *Nigella sativa* L seeds. *J Ethnopharmacol*, **70(1):** 1-7(2000).
98. Hong-Bing Wang, Hui Yao, Guan-Hu Bao, Hua-Ping Zhang and Guo-Wei Qin, Flavone glucosides with immunomodulatory activity from the leaves of *Pleioblastus amarus*. *Phytochemistry*. **65:** 969–974(2004).
99. Sun-A Im , Kyungjae Kim and Chong-Kil Lee. Immunomodulatory activity of polysaccharides isolated from *Salicornia herbacea. International Immunopharmacology* **6:** 1451–1458 (2006).
100. S. K. Katiyar. Silymarin and skin cancer prevention: Anti-inflammatory, antioxidant and immunomodulatory effects. *Int J Oncol*. **26:**169-76(2005).
101. G. Deak, G Muzes and I. Lang. Immunomodulator effect of silymarin therapy in chronic alcoholic liver diseases. *Orv. Hetil.* **131:** 1291-1292, 1295-1296(1990).
102. I. Lang, K. Nekam and R. Gonzalez-Cabello. Hepatoprotective and immunological effects of antioxidant drugs. *Tokai J Exp Clin Med.* **15:**123-127(1990).
103. L. Kalmar, J. Kadar and A. Somogyi, Silibinin (Legalon-70) enhances the motility of human neutrophils immobilzed by formyl-tripeptide, calcium ionophore, lymphokine and by normal human serum. *Agents and Actions*, **29:** 239-246(1990).
104. F. Minonzio, E. Venegoni and A. Ongari, Modualtion of human polymorphonuclear leukocyte function by the flavonoid silybin. *Int J Tiss Reac*. **4:** 223-231(1988).
105. E. Leng-Peschlow, Properties and medical use of flavonolignans (Silymarin) from *Silybum marianum. Phytotherapy Research*. **10:**S25-S26 (1996).
106. I. Lang, K. Nekam, R. Gonzalez-Cabello, G. Muzes, P. Gergely and J. Feher. Hepatoprotective and immunological effects of antioxidant drugs. *Tokai J Exp Clin Med.* **15:** 123-7(1990).
107. C. Wilasrusmee, S. Kittur, G. Shah, J. Siddiqui, D. Bruch, S. Wilasrusmee and D. S. Kittur, *Int J Oncol*. **21(6):** 1213-22(2002).
108. S. S. Singh, S. C. Pandey, S. Srivastava, V. S. Gupta, B. Patro and A. C. Ghosh. Chemistry and medicinal properties of *Tinospora cordifolia, Indian Journal of Pharmacology*. **35:** 83-91 (2003).
109. A. Kapil and S. Sharma. Immuno potentiating compounds from *T. Cordifolia. J. Ethnopharmacol*. **58:** 89-95(1997).

110. N. N. Rege, U. M. Thatte and S. A. Dahanukar. Adaptogenic properties of six rasayana herbs used in ayruvedic medicine. *Phytother Res.* **13:** 275-91(1999).
111. V. Wazir, R. Maurya and R. S. Kapil, Cordioside, a clerodane furano diterpene glucoside from *T. cordfolia*. *Phytochemistry.* **38:** 447-449(1995).
112. A. Kapil, R. Shah and S. Sharma. Immunopotentiating and anticomplementary activity of fungisterol from mushroom *Suillus sibiricus*. *Indian Drugs*. **31:** 525 527(1994).
113. S. Diwanay, D. Chitre and B. Patwardhan. Immuno protection by botanical drugs in cancer chemotherapy. *Journal of Ethnopharmacology*. **90:** 49–55(2004).
114. A. Kapil S. Sharma. Immuno potentiating compounds from *Tinospora cordifolia*. *J.ethno pharmacol.* **58:** 89-95(1997).
115. J. Eck, M. Langer, B. Mockel, K. Witthohn, H. Zinke and H. Lentzen. Characterization of recombinant and plant-derived mistletoe lectin and their B-chains. *Eur J Biochem* **265:** 788–797(1999).
116. P. W. Joller, J. M. Menrad, T. Schwarz, U. Pfüller, M. J. Parnham, R. Weyhenmeyer and H. Lentzen. Stimulation of cytokine production via a special standardized mistletoe preparation in an *in vitro* human skin bioassay. *Arzneim-Forsch/Drug Res* **46:** 649–653(1996).
117. M. Ziauddin, et al. Studies on the immunomodulatory effects of Ashwagandha. *J Ethnopharmacol,* **50:** 69(1996).
118. R. Agarwal, et al. Studies on immunomodulatory activity of *Withania somnifera* (Ashwagandha) extracts in experimental immune inflammation. *J Ethnopharmacol*, **67:** 27(1999).
119. L. Davis, G. Kuttan, Suppressive effect of cyclophosphamide toxicity models in normal animals induced toxicity by *Withania somnifera* extract in mice. *Journal of Ethnopharmacology*. **62:** 209–214(1998).
120. G. Kuttan. Use of Withania somnifera Dunalas an adjuvant during radiation therapy. *Indian Journal of Experimental Biology,* **34:**854–856(1996).
121. L. Davis, G. Kuttan, Effect of Withania somnifera on cytokine production in normal and cyclophosphamide treated mice. *Immunopharmacology and Immunotoxicology.* **21:** 695–703(1999).
122. M. al Hindawi, et al, Anti-inflammatory activity of some Iraqi plants using intact rats, *J Ethnopharmacol,* **26:** 163(1989).
123. M. al Hindawi, et al, Anti-granuloma activity of Iraqi *Withania somnifera*. *J Ethnopharmacol,* **37:** 113(1992).
124. V. Bähr, et al. Immunomodulating properties of 5,20-alpha(R)-dihydroxy-6-alpha-7-alpha-epoxy-1-oxo-(5-alpha)-witha-2,24-dienolide and solasodine. *Planta Med,* **44:** 32(1982).
125. J. Dhuley, Effect of some Indian herbs on macrophage functions in ochratoxin A treated mice. *J Ethnopharmacol,* **58:** 15(1997).
126. S. Ghosal, et al. Immunomodulatory and CNS effects of sitoindosides IX and X, two new glycowithanolides from *Withania somnifera* . *Phytother Res.* **3:** 201(1989).
127. J. Dhuley. Therapeutic efficacy of Ashwagandha against experimental aspergillosis in mice. *Immunopharmacol Immunotoxicol.* **20:** 191(1998).
128. S. Ghosal, J. Lal, R. Srivastava, et al. Immunomodulatory and CNS effects of sitoindosides IX and X, two new glycowithanolides from *Withania somnifera*. *Phytotherapy Res*. **3:** 201-206(1989).
129. Y. Lu, J. Fan, Y. Zhao, S. Chen, X. Zheng, Y. Yin and C. Fu. Immunomodulatory activity of aqueous extract of *Actinidia macrosperma*, *Asia Pac J Clin Nutr.* **16 (11):** 261-265(2007).
130. S. F. Egger, G. S. Brown, L. S. Kelsey, K. M. Yates, L. J. Rosenberg and J. E. Talmadge, *Int J Immunopharm.* 1**8(2):** 113-126(1996).
131. N. Pugh, S. A. Ross, M. A. ElSohly, D. S. J. Pasco, Agric. *Food Chem*. Characterization of Aloeride, a new high-molecular-weight polysaccharide from *Aloe vera* with potent immunostimulatory activity. **49:** 1030-1034 (2001).
132. M. L. Sharma, A. Kaul and A. Khajuria, et al. Immunomodulatory activity of Boswellic acids (Pentacyclic Triterpene Acids) from *Boswellia serrata. Phytotherapy Res*, **10:** 107-112(1996).
133. F. Badria, B. R. Mikhaeil, G. T. Maatooq and M. M. A. Amer , Immunomodulatory Triterpenoids from the Oleogum Resin of *Boswellia carterii* Birdwood, Z. *Naturforsch.* **58:** 505-516 (2003).
134. Z. Amirghofran, M. Azadbakht and M. H. Karimi. Evaluation of the immunomodulatory effects of five herbal plants. *Journal of Ethnopharmacology* **72:** 167–172(2000).
135. M. Thakur, S. Bhargava and V. K. Dixit. Immunomodulatory Activity of *Chlorophytum borivilianum Sant.F. eCAM* 1-5(2006).
136. E. Zvetkova , B. Wirleitner, N.T. Tram , H. Schennach and D. Fuchs. Aqueous extracts of *Crinum latifolium* and *Camellia sinensis* show immunomodulatory properties in human peripheral blood mononuclear cells. *International Immunopharmacology* **1:** 2143–2150(2001).
137. Y. C. Jae, R. K. Ae, S. Y. Eun, U. B. Kyong and H. P. Myung. Ginsenosides from Panax ginseng differentially regulate lymphocyte proliferation. *Planta Med.* **6:** 497-500(2002).
138. S. Bani, A. Kaul, B. Khan, V. K. Gupta, N. K. Satti, K. A. Suri and G. N. Qazi. Anti-arthritic activity of a biopolymeric fraction from *Euphorbia tirucalli*. *Journal of Ethnopharmacology*. **110(1):** 92-98(2007).
139. S. Y. Gabhe, P. A. Tatke and T. A. Khan. Evaluation of the immunomodulatory activity of the methanol extracts of *Ficus benghalensis* roots in rats. *Indian J Pharmacol,* **38:** 271-275(2006).
140. Y. Y. Wang, K. H. Khoo, S. T. Chen, C. C. Lin, C. H. Wong and C. H. Lin. Studies on the Antitumor Activity of Ganoderma Lucidum (Reishi) Polysaccharides: Functional and Proteomic Analysis of a Fucose-containing Glycoprotein Responsible for the Activity. *Bioorg and Med Chem.* **10(4):** 1057-1062(2002).
141. Bernadete Pereira da Silva, Jos´e Paz Parente. An anti-inflammatory and immunomodulatory polysaccharide from *Orbignya phalerata, Fitoterapia* **72:** 887-893 (2001).
142. L. A. D. Williams, T. L. The, M. T. Gardner, C. K. Fletcher, A. Naravane, N. Gibbs and R. Fleishhacker. Immunomodulatory activities of *Petiveria alliacea* L. *Phytotherapy Research*. **11(3):** 251-253(1997).
143. Y. C. Kuo, L. C. Lin, N. S. Yang, W. J. Tsai, A. P. Lin, M. J. Lee and C. J. Chou. Some immunomodulatory Principles isolated from *Piper kadsura*. *J Chin Med.* **13(3):** 159-170(2002).
144. E.S. Sunila and G. Kuttan. Immunomodulatory and antitumor activity of *Piper longum* Linn. and piperine. *Journal of Ethnopharmacology* **90:** 339–346(2004).
145. Y. Sato, S. Suzaki, T. Nishikawa, M. Kihara, H. Shibata and T. J. Higuti, *Ethnopharm.* **72:** 483-488(2000).
146. H. C. Jen, S. L. Ing, Y. S. Ming, L. C. Hsiu, C. C. Ai, Y. L. Wing and W. W. Chew, *Planta Med.* **68:** 1036-1039(2002).
147. B. K. H. Tan and J. Vanitha, Immunomodulatory and Antimicrobial Effects of Some Traditional Chinese Medicinal Herbs: A Review , *Current Medicinal Chemistry*, **11:** 1423-143