A review on immunostimulatory plants

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Abstract: The use of medicinal plants to cure human illness has been practiced from time immemorial. Nowadays, the vast majority of people still rely on their traditional materia medica for their daily health care needs. The use of plant species for treatment of various human ailments has been mentioned in Ayurveda and other Indian literature. Some of these drugs are believed to enhance the natural resistance of body to infection. So there are many plants having immunostimulatory activity. This paper reviews plants which have shown reported immunostimulatory activity.

Keywords: adjuvants, immunologic; plants, medicinal; review

Immunomodulation is the regulation and modulation of immunity either by enhancing or by reducing the immune response. Modulation of immune response may involve induction, expression or amplification of immune response. In other words, immunomodulation involves a change in the human body’s immune system caused by agents that activate or suppress its function. If the modulation in immune system results in enhancement of immune reaction, it is known as the immunostimulation. There are two main categories of immunostimulators. The specific immunostimulators are those which provide antigenic specificity in immune response, such as vaccines or any antigen; the non-specific immunostimulators are those which act irrespective of antigenic specificity to augment immune response of other antigens or stimulate components of the immune system without antigenic specificity, such as adjuvants and non-specific immunostimulators. In terms of immunostimulant substances used in the general human population, the vaccines are the most commonly employed. Vaccines are used to stimulate a protective immune response to antigens from specific pathogens. Another type of immunostimulant which is called the adjuvant is often used in conjunction with vaccines. Adjuvants are a type of non-specific immunostimulant. Administering an adjuvant along with a vaccine helps to generate a stronger protective response to the antigens in the vaccine, providing a better degree of protection against the pathogen. Many substances produced by the human body function as immunostimulants. Cytokines are a type of immunostimulant, which are produced by the cells of the immune system, and many have a role in enhancing immune function. Hence, both immunostimulating agents and immunosuppressing agents have their own importance, and searching for better agents exerting these activities is becoming increasingly more successful.

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a field of interest all over the world[41]. Various natural adjuvant and synthetic agents are used as immunostimulatative agents, such as levamisole, thalidomide, but there are various side effects of these agents such as nephrotoxicity, hepatotoxicity, bone marrow depression, gastrointestinal disturbances, hypertension, hirustism, myalgia and so on. Because of these side effects associated with the synthetic drugs and as plants are safer, cheaper and much more effective, conventional immunomodulator plants can be explored[42]. Traditional Indian system of medicines like Siddha and Ayurveda has also suggested means to increase the body’s natural resistance to diseases. A number of Indian medicinal plants and various rasayas was have been claimed to possess immunostimulatory activity[43, 44]. In the present review, we will focus on various plants having immunostimulatory activity.

1 Immunostimulatory plants

1.1 Actinidia macrospora Actinidia macrospora, commonly known as kiwifruit, belongs to the family Actinidiaceae and is distributed all over the world, especially in East Asia. Traditionally it has been used to treat different cancers, including those of the digestive system and mammary gland[45]. There is a renewed interest in its chemical compositions and biological activities. A number of bioactive constituents have been reported, including polysaccharides[46], alkaloids[47], saponins[48] and organic acid. It has been extensively employed to treat various ailments such as leprosy, abscess, rheumatism, arthritis inflammation, jaundice, abnormal leucorrhoea and so on[49]. It has also been reported that Actinidia macrospora was useful for the treatment of cancers, especially those of the lung, liver and digestive system. The immunostimulatory effects of aqueous extract of Actinidia macrospora were examined by using SI80-bearing mice. The results showed that the aqueous extract of Actinidia macrospora was lack of significant inhibition on transplantable sarcoma SI80, with a inhibition rate of 1.5% to 14.8% (an optimal dose at 250 mg/kg), but significantly increased the overall immune functions (especially at 100 and 250 mg/kg). The immunostimulatory effect was dose-dependent in a nonlinear fashion with the optimal dose of 100 mg/kg[50].

1.2 Aesculus indica Aesculus indica belonging to the family Sapindaceae is a herbaceous, soft perennial plant abundantly found in northwestern Himalayas. Generally it is called as Bankhhor[51]. A study has shown the immunostimulatory effect of Aesculus indica, and rats were used for this investigation. Extracts of Aesculus indica were administered orally at 50 and 100 mg/kg to healthy rats divided into five groups consisting of six animals each. The assessment of immunostimulatory activity was carried out by testing the humoral (antibody titer) and cellular (foot pad swelling) immune responses to the antigenic challenge by sheep red blood cells (SRBCs) and by neutrophil adhesion test. On oral administration of the extracts, significant increases in neutrophil adhesion and delayed type hypersensitivity (DTH) response were observed whereas the humoral response to SRBCs was unaffected. Thus Aesculus indica significantly potentiated the cellular immunity by facilitating the foot pad thickness responses to the SRBCs in sensitized rats. With doses of 50 or 100 mg/kg, the DTH response was statistically significant compared with the control. The study stated that Aesculus indica could stimulate the cell-mediated immunity and had no effects on the humoral immunity[52].

1.3 Allium sativum Allium sativum (family Liliaceae) was commonly known as aslan. Organosulphur compounds of garlic have been shown to inhibit growth of tumours in animals and to modulate activity of diverse chemical carcinogens[53]. This effect may be related to the activation of natural killer (NK) cells, stimulation of T lymphocytes and enhanced production of interleukin (IL)-2. Garlic extract has been shown to enhance cytotoxicity of human peripheral blood lymphocytes against both NK cell sensitive (K562) and resistant (M14) cell lines[54]. It has also demonstrated that garlic may augment macrophage (oxidative burst) and T lymphocyte (blastogenesis) functions. Garlic extract could also protect from ultraviolet-induced suppression of contact hypersensitivity[55].

1.4 Aloe vera Aloe vera (family Liliaceae; synonym: Aloe barbadensis) is one of the most widely used healing plants in the history of mankind. Aloe vera is used in traditional medicine of many cultures and said to be beneficial in the treatment of disorders such as arthritis, gout, dermatitis, peptic ulcer and burns[56]. Aloe vera gel (AVG) is one of the few substances known to effectively decrease inflammation and promote wound healing[57]. A recent study has shown that short term exposure of macrophage to acemannan up-regulates the respiratory burst, phagocytosis and candidicidal activity. Acemannan is the major carbohydrate fraction obtained from the AVG. Macrophage activation may be accountable for immunostimulating effect of acemannan. It may be responsible for regression of tumors in experimental animals. It could also increase lymphocyte responses to alloantigen via IL-1 production, which may explain its capacity to abrogate viral infections in animals and man[58].

1.5 Andrographis paniculata Andrographis paniculata is traditionally known as kalmegh. It belongs to the family Acanthaceae and is widely used in Ayurvedic and homeopathic systems of medicine. Mice studies have shown that Andrographis paniculata is a potent stimulator of the immune system in two ways, namely, the antigen-specific
response that antibodies are made to counteract invading microbes, and non-specific immune response that 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. Ethanolic extract of *Andrographis paniculata* induced significant stimulation of antibody and DTH response to SRBCs in mice\[^{18}\]. The immunomodulatory activity of HN-02, an extract containing a mixture of andrographolides in a pure powder form, was evaluated at 1.0, 1.5 and 2.5 mg/kg on different in vivo and in vitro experimental models. In a DTH mouse model, potentiation of the DTH reaction was observed after treatment with cyclophosphamide and HN-02 individually\[^{10}\]. Compounds isolated from *Andrographis paniculata* had also shown anticancer and immunostimulatory activities\[^{20}\].

1.6 *Asparagus racemosus* Immunostimulating property of *Asparagus racemosus* (family Liliaceae) has been shown to protect the rats and mice against experiment-induced abdominal sepsis\[^{21}\]. Oral administration of decoction of powdered root of *Asparagus racemosus* has been reported to produce leukocytosis and predominant neutrophilia along with enhanced phagocytic activity of the macrophages and polymorphs. Percentage mortality of *Asparagus 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 gentamycin\[^{22}\]. Since *Asparagus racemosus* is reported to be devoid of antibacterial action, protection offered by it against sepsis by altering function of macrophages indicates its possible immunostimulatory property\[^{21}\]. Further, oral administration of total extract of *Asparagus 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. Dhuley\[^{23}\] has reported the revival of macrophage chemotaxis and reduction of IL-1 and tumor necrosis factor (TNF)-α by the oral treatment of *Asparagus racemosus* root extract in an ocratoxin-treated mouse model. Alcoholic extract has been found to enhance both humoral and cell-mediated immunity of albino mice injected with SRBCs as particulate antigen\[^{21}\].

1.7 *Asadirachta indica* *Asadirachta indica* (family Meliaceae), a native tree of India growing in tropical climate, has been widely used in Indian system of Ayurvedic medicine for various therapeutic purposes such as curing ulcers, skin infections, asthma, diabetes, rheumatism etc\[^{24}\]. 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. Neem oil acts as a non-specific immunostimulant and it selectively activates the cell-mediated immune mechanisms to elicit an enhanced response to subsequent mitogenic or antigenic challenges. Recently, an aqueous extract of the stem bark has been shown to enhance the immune response of BALB/c mice to SRBCs in vivo. Leaves extract at 100 mg/kg after three weeks of oral administration caused higher IgM and IgG levels along with increased titer of antiovalbumin antibody\[^{25}\]. NIM-76, a fraction isolated from the neem oil, has immunostimulatory properties. The initial response of NIM-76 treatment appears to activate macrophages and promote T lymphocyte proliferative responses. Crude neem oil after intraperitoneal administration into the mice stimulated the T cells to produce interferon (IFN)-γ which in turn stimulate macrophages. Significant restriction of growth of Ehrlich’s carcinoma was observed following prophylactic treatment on Swiss albino mice with neem leaf preparations (NLP-1 unit) once weekly for four weeks\[^{26}\]. Neem extract has also shown as an immunostimulant in fresh water fish. The leaf preparation has been used as an adjuvant to enhance the efficacy of poorly immunogenic B16 melanoma surface antigen vaccine\[^{27,28}\].

1.8 *Baliospermum montanum* *Baliospermum montanum* of the family Euphorbiaceae is a stout under shrub with herbaceous branches from the roots. An aqueous extract of roots of *Baliospermum montanum* was evaluated on preliminary basis for immunostimulatory activity by studying neutrophil phagocytic function. The different concentrations (25, 50 and 100 µg/mL) of aqueous extract of roots of *Baliospermum montanum* were subjected to study their effects on different in vitro methods of phagocytosis such as neutrophil locomotion, chemotaxis, immunostimulant activity of phagocytosis of killed *Candida albicans* and qualitative nitroblue tetrazolium test by using human neutrophils. This preliminary study revealed that *Baliospermum montanum* extract has stimulated chemotactic, phagocytic and intracellular killing potency of human neutrophils at different concentrations. From the results obtained, it can be observed that the aqueous extract of *Baliospermum montanum* stimulate cell-mediated immune system by increasing neutrophil function\[^{29}\].

1.9 *Boerhaavia diffusa* *Boerhaavia diffusa* is an abundant creeping weed found all over India. Treatment with aqueous extract of *Boerhaavia diffusa* roots has been shown to induce leukocytosis with predominant neutrophilia, associated with a stimulation of the phagocytic and bactericidal capacity of neutrophils and macrophages. The aqueous extract also protected mice against *Escherichia coli*-induced peritonitis based on its immunostimu-
latory activity. A study has also shown in vivo immunostimulatory activity of *Boerhaavia diffusa* without in vitro effect where alkaloidal fraction of *Boerhaavia diffusa* was studied for its effect on cellular and humoral functions in mice. Oral administration of the fraction (25 to 100 mg/kg) significantly inhibited SRBC-induced DTH reactions in mice. A significant dose-related increase in antibody titer was observed during pre- and post-immunization treatment.\(^{10}\)

1. **Boswellia carterii** *Boswellia carterii* or *Boswellia serrata* belongs to the family Burseraceae. An extracted resin, salai guggal, is produced predominantly by four species, including *Boswellia serrata* in India. This salai guggal has been shown to exhibit strong immunostimulant activity.\(^{11}\)

The active constituents are contained in the extracted *Boswellia* terpenoid portion and are composed of boswellic acids (BAs). The ethanol extract was then tested for its ability to alter in vitro production of T helper 1 (Th1) cytokines (IL-2 and IFN-\(\gamma\)) and Th2 cytokines (IL-4 and IL-10) by murine splenocytes. Delivery of the resin extract using ethanol as a solvent resulted in significant cellular toxicity which was not seen with the addition of ethanol alone. By contrast, delivery of the resin extract using a sesame oil solvent resulted in a dose-dependent inhibition of Th1 cytokines coupled with a dose-dependent potentiation of Th2 cytokines. These results indicated that a purified mixture of BAs from *Boswellia carterii* plant resin exhibited carrier-dependent immunostimulatory properties in vitro.\(^{12}\)

1. **Capparis zeylanica** *Capparis zeylanica* (family Capparidaceae) is commonly known as Indian caper, is a climbing shrub found throughout India and has been used as a rasayana drug in the traditional Ayurvedic system of medicine. Rasayana plants are particularly recommended for the treatment of immune disorders.\(^{13}\) A study was therefore undertaken to explore the preliminary phytochemical screening, acute toxicity, immunostimulatory activity of ethanolic and water extracts of *Capparis zeylanica* leaves on cellular and humoral immune responses to the antigenic challenge by SRBCs and by neutrophil adhesion test, phagocytic activity and cyclophosphamide-induced myelosuppression. Pretreatment of water extract (300 mg/kg orally) of *Capparis zeylanica* evoked a significant increase in neutrophil adhesion to nylon fibers. The augmentation of humoral immune response to SRBCs by ethanolic and water extracts (150 to 300 mg/kg) was evidenced by increase in antibody titers in mice. A dose-related increase in both primary and secondary antibody titer was observed. Oral administration of ethanolic and water extracts of *Capparis zeylanica* leaves, at doses of 150 and 300 mg/kg in mice, dose-dependently potentiated the DTH reaction induced by SRBCs. Immunostimulatory activity was also assessed by serological and haematological tests. *Capparis zeylanica* extracts prevented myelosuppression in mice treated with cyclophosphamide drug.\(^{14}\)

1. **Caesalpinia bonduc** *Caesalpinia bonduc* (family Caesalpiniaceae) is a plant well-known for its medicinal value in Indian Ayurveda. It possesses potential immunostimulatory activity and has therapeutic potential for the prevention of autoimmune diseases. The evaluation of immunostimulatory potential by oral administration of ethanolic seed extract of *Caesalpinia bonduc* (200 to 500 mg/kg) evoked a significant increase in percent neutrophil adhesion to nylon fibers as well as a dose-dependent increase in antibody titer values, and potentiated the DTH reaction induced by SRBCs. It also prevented myelosuppression in cyclophosphamide drug-treated rats and showed good response towards phagocytosis in carbon clearance assay.\(^{15}\)

1. **Centella asiatica** *Centella asiatica* (family Apiaceae) is a perennial creeper, growing abundantly in moist areas and distributed widely in tropical and subtropical countries. The reticuloendothelial stimulating activity of the alcoholic extract of *Centella asiatica* and an increase in the antibody titer and cell-mediated response (DTH) at 100 mg/kg body weight of dried powder of *Centella asiatica* have been reported.\(^{16}\)

1. **Chlorella vulgaris** *Chlorella vulgaris* (family Chlorophyceae) is suitable for protein products sold as health foods and food supplements. A study was designed to examine the effects of oral administration of an enzymatic protein hydrolysate from green micro-alga *Chlorella vulgaris* (Cv-PH) on the recovery of both innate and specific immune responses of undernourished BALB/c mice after a 3-day fasting period. The treatment with Cv-PH (500 mg/kg) for 8 d provided benefits in terms of haemopoiesis, as judged by the recovery of bone marrow cellularity and the leucocyte counts in peripheral blood, particularly the lymphocyte pool, which increased up to 128% compared with the control animals. The increased carbon clearance in peripheral blood suggested the stimulation of mononuclear phagocytic system. Cv-PH also stimulated both humoral and cell-mediated immune functions positively, such as T-dependent antibody response and the reconstitution of DTH response. These findings indicated that *Chlorella* protein hydrolysate can be used for developing physiologically functional foods with immunostimulating activity.\(^{17}\)

1. **Chlorophyllum borivilianum** *Chlorophyllum borivilianum* (family Liliaceae) is a very popular herb in traditional Indian medicine and constitutes a group of herbs used as a rasayana or an adaptogen. Ethanol extract of the roots and its sapogenin were evaluated for their immunostimulatory activity.
Effect of administration of extracts on azathioprine-induced myelosuppression and the hematological and serological parameters were determined. Administration of the extracts greatly improved survival against *Candida albicans* infection. Increases in DTH response, percent of neutrophil adhesion and in vivo phagocytosis by carbon clearance method were observed after treatment with the extracts. Immunostimulant activity of ethanolic extract was more pronounced as compared with sapogenins. The results justified the traditional use of *Chlorophyllum borivilianum* as a rasayana drug[41].

1.16 Clerodendrum phlomisdis *Clerodendrum phlomisdis* belongs to the family Verbanaceae and its common name is Arni in Ayurveda. Its roots are important ingredient of Ayurvedic preparations such as Dashmool Kwaitha, Chyanprashavleh, Haritakivle, Ayushyavardhak Tel, Narayan Tel and so on, valued for the treatment of a variety of affections. *Clerodendrum phlomisdis* is a large bush or a small tree, growing throughout India. Roots are valued as tonic, diuretic, febrifuge, antidiabetic, anti-inflammatory and antiulcerative[42]. A study has shown immunostimulatory potential of roots of this plant. Oral administration of methanol extract of roots in mice prior to immunization with SRBCs resulted in significant increase in haemagglutinating antibody titer, plaque-forming cell (PFC) assay and DTH to SRBCs. *Clerodendrum phlomisdis* enhanced the non-specific immune response in carbon clearance test and showed significant immunophylactic effect, when tested on *Escherichia coli*-induced abdominal sepsis[43].

1.17 Curculigo orchoides *Curculigo orchoides* belongs to the family Amaryllidaceae. Methanolic extract of the roots has been shown to enhance phagocytic activity of macrophages and an active principle of the extract was identified as a curculigoside, which has been reported to possess adjuvant activity[44]. Its rhizomes had yielded a phenolic glycoside named orchiroside A[45], in addition to a few triterpene glycosides. These glycosides were studied for their effects on macrophage migration index (MMI), haemagglutination (HA) titer, PFC, phytohemagglutinin (PHA)-induced blast transformation of lymphocytes (BTL) and DTH. Significant immunostimulant activity was found in purified glycoside-rich fraction isolated from the ethyl acetate extract. The exact structure of the active glycoside was yet to be determined. The enhancement of HA titer and PFC count on one hand and that of DTH response on the other indicated that glycoside fraction stimulates both humoral and cell-mediated immune responses. Glycoside fraction stimulated immune response by acting both on macrophages and the lymphocytes[46].

1.18 Curcuma longa *Curcuma longa*, a perennial herb of the Zingiberaceae family, contains 0.3% to 5.4% curcumin (one of the major curcuminoids) depending on the season of its harvest[47]. 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), PHA, and phorbol-12-myristate-13-acetate (PMA) of lymphocytes derived from fresh human spleen[48].

1.19 Eclipta alba *Eclipta alba* (family Asteraceae) is called “Bhringraj” in India. In traditional medicine, whole dried herb powder is used in liver disorders, especially jaundice[49]. The herb contains wedelolactone and dimethylweddolactone as coumestan derivatives and recently, a triterpenoidal saponin named eclabatin, has also been isolated from this plant[50]. *Eclipta alba* increased the phagocytic index and antibody titer significantly and the F ratios of the phagocytic index and white blood cell (WBC) count are also significantly increased when it was tested by using carbon clearance, antibody titer and cyclophosphamide-induced immunosuppression.

1.20 Emblica officinalis *Emblica officinalis*, commonly known as Amla (family Euphorbiaceae), is extensively found all over India, as well as Sri Lanka, Malaya, China, Pakistan, and Bangladesh. Despite many therapeutic effects of Amla, it also shows immunostimulatory effects on lymphocyte function, particularly in immunosuppressive conditions. Therefore, an *in vitro* study was undertaken to determine the relative effects of fruit extracts of Amla with regard to cytoprotection and immunostimulation by using rat splenocytes as the model system. Immunostimulatory properties of Amla are determined by using chromium (VI) as an immunosuppressive agent. Amla inhibited apoptosis and DNA fragmentation induced by chromium. Interestingly, Amla relieved the immunosuppressive effects of chromium on lymphocyte proliferation and even restored the IL-2 and g-IFN production considerably[51].

1.21 Epilobium angustifolium *Epilobium angustifolium* (family Onagraceae) has been traditionally used in the treatment of a number of diseases; however, not much is known regarding its effect on innate immune cells. In a recent study, it has reported that extracts of *Epilobium angustifolium* activated functional responses in neutrophils and monocyte/macrophages. Activity-guided fractionation, followed by mass spectroscopy and nuclear magnetic resonance analysis, resulted in the identification of oenothein B as the primary component responsible for phagocyte activation. Oenothein B, a dimeric hydrolysable tannin, dose-dependently induced a number of phagocyte functions *in vitro*, including intracellular Ca²⁺ flux, production of reactive oxygen species, chemotaxis,
nuclear factor (NF)-κB activation, and proinflammatory cytokine production. Furthermore, oenothine B was active in vivo, inducing keratinocyte chemotactrant production and neutrophil recruitment to the peritoneum after intraperitoneal administration. The ability of oenothine B to modulate phagocyte functions in vitro and in vivo suggested that this compound was responsible for at least part of the therapeutic properties of Epilobium angustifolium extracts[52].

1.22 Ficus benghalensis An aqueous decoction of the fresh aerial roots of the Indian banyan, named Ficus benghalensis (family Moraceae) has been used by Ayurvedic medical practitioners to boost the immune system in various diseases. A recent study is an effort to scientifically evaluate the immune-bolting potential of the aqueous extract of the aerial roots of the Indian banyan. The aqueous extract of the aerial roots of Ficus benghalensis was evaluated for its effect on both specific and non-specific immunity. This extract significantly increased the percentage phagocytosis by human neutrophils in in vitro tests. It exhibited promising immunostimulant activity at 50, 100, 200 and 400 mg/kg body weight in SRBCs-induced hypersensitivity reaction and hemagglutination reaction in rats. The aqueous extract was found to stimulate the cell- and antibody-mediated immune responses[53].

1.23 Gymnema sylvestre Gymnema sylvestre (family Asclepiadaceae) leaves, commonly known as Gudmar, is a large woody, much branched climber with pubescent young parts in dry forest up to 600 meters high[54]. Tannins are the main chemical constituents present in Gymnema sylvestre and are known to possess anti-inflammatory and immunomodulatory properties[55]. The aqueous extract of Gymnema sylvestre leaves was investigated for immunostimulatory activity by assessing neutrophil locomotion and chemotaxis test, phagocytosis of killed Candida albicans and nitroblue tetrazolium tests. The extract was given at 10, 25, 50, 100 and 1 000 μg/mL. Results of in vitro immunostimulatory activity lead to the conclusion that the aqueous extract of Gymnema sylvestre showed predominantly significant activity on in vitro human neutrophils in all parameters as compared with the standard[56].

1.24 Heracleum nepalense Heracleum nepalense (family Apiaceae) is a small shrub which grows in Nepal and Sikkim. It is used in veterinary medicine. It exhibited stimulant property and increased the rate of respiration and blood pressure in goats[57]. An investigation was undertaken to evaluate the immunostimulatory potential of Heracleum nepalense roots by using in vitro and in vivo models. The immunostimulatory potential of this plant was investigated by in vitro phagocytic index and lymphocyte viability tests, using IFN-α-2b, a known immunostimulant drug, as the standard. Other tests such as carbon clearance, antibody titer and DTH were studied in mice by using levimazole as the standard. The dried root extract (1 000 μg/mL) and isolated quercetin glycoside (50 μg/mL) significantly increased the in vitro phagocytic index and lymphocyte viability in all assays. They also showed a significant increase in antibody titer, carbon clearance and DTH in mice. Thus Heracleum nepalense exhibited a dose-dependent immunostimulant effect, which could be attributed to the flavonoid content or due to the combination with other components[58].

1.25 Janakia arayalpathra Janakia arayalpathra (family Periploaceae) is a perennial woody laticiferous shrub[59]. Recent pharmacological investigations of the root extract of the plant revealed immunostimulatory and anticancer properties. It stimulated an increase in humoral antibody titers and also of antibody-secreting spleen cells in the PFC assay following immunization with sheep erythrocytes. It also increased the number of peritoneal macrophages and produced an increase in DTH reaction in mice[60].

1.26 Mangifera indica Mangifera indica (family Anacardiaceae) is commonly known as mango. It has been reported for its in vitro immunostimulatory activity. The alcoholic extract of the stem bark containing 2.6% of mangiferin had promising in vivo immunostimulatory effect. Further it was confirmed that the immunostimulatory effect was due to cell- and humoral antibody-mediated activation of T and B cells[61].

1.27 Morinda citrifolia Morinda citrifolia (family Rubiaceae) was evaluated for the immunostimulant effects. The extract and the fraction were evaluated for their effects on in vitro phagocytosis of Candida albicans spores by neutrophils obtained from pooled human blood. The maximum activity was demonstrated by the hydroalcoholic extract (79.25% at 1.0 mg/mL, P<0.05) and the polysaccharide fraction (60.0% at 0.2 mg/mL, P<0.05) obtained from the fruits of the plant. The hydroalcoholic extract and the polysaccharide fraction were evaluated for their effects on serum IL-6 level in rats sensitized by intraperitoneal injection of Bacillus Calmette-Guerin (BCG) vaccine intraperitoneally. The hydroalcoholic extract (910.82 pg/mL at 200 mg/kg, P<0.05) and the polysaccharide fraction (556.82 pg/mL at 40 mg/kg, P<0.05) significantly increased serum IL-6 level in the antigenically challenged rats as compared with the vehicle control group (75.04 pg/mL) and standard reference herbal drug, Withania somnifera L. Dunal (Solanaceae) (396.38 pg/mL). The studies indicated the potential of Morinda citrifolia as an immunostimulant herbal drug[62].

1.28 Nyctanthes arbortristis Nyctanthes arbortristis
agent\textsuperscript{[41]}. A 50% ethanolic extract of *Picrorhiza kurroa* Royle ex Benth. (Scrophulariaceae) leaves (PKLE) was found to stimulate the cell-mediated and humoral components of the immune system as well as phagocytosis in experimental animals. PKLE elicited a dose-related increase in SRBCs, induced 4 h (early) and 24 h (delayed) hypersensitivity reactions in mice and rats, and horse serum-induced Arthus reaction in guinea pigs. It also enhanced the humoral immune responses in mice and rats and phagocytic function of the cells of the reticuloendothelial system in mice. PKLE exhibited no mitogenic activity but augmented the responsiveness of murine splenocytes to T cell mitogens PHA and Con A, and B cell mitogen lipopolysaccharide\textsuperscript{[26]}. A 32 *Piper longum* *Piper longum* (family Piperaceae) as an important medicinal plant, is used in traditional medicines by many people in Asia and Pacific islands especially in Indian medicine\textsuperscript{[27]}. Alcoholic extract of the fruits of *Piper longum* and its component piperine were studied for their immunostimulatory activity. Administration of *Piper longum* extract and piperine increased the total WBC count to 142.8\% and 138.9\% respectively, in BALB/c mice. The number of PFC was also enhanced significantly by the administration of the extract (100.3\%) and piperine (71.4\%) on the 5th day after immunization. Bone marrow cellularity and esterase positive cells were also increased by the administration of *Piper longum* extract and piperine\textsuperscript{[28]}. A 33 *Randia dumentorum* *Randia dumentorum* (Rubiaceae) is known as Madana (Sansk.), or Mainphal (Hindi). In the Ayurvedic texts, *Randia dumentorum* is classified as a drug having properties similar to the rasayanas\textsuperscript{[29]}. An attempt was made to screen the immunostimulatory activity of the methanol extract and its petroleum ether, chloroform, ethyl acetate and methanol fractions of fruits of *Randia dumentorum*. The effects of *Randia dumentorum* on cell-mediated and humoral components of the immune system in mice were observed. Administration of the chloroform fraction at 100 mg/kg produced statistically significant results as evidenced by the increase in the humoral antibody titer, DTH response. This fraction also enhanced the total WBC level in cyclophosphamide-induced myelosuppression model at 100 mg/kg. Petroleum ether fraction and methanol fraction only affected cell-mediated immunity\textsuperscript{[24]}. A 34 *Salicornia herbacea* Immunostimulatory polysaccharides isolated from *Salicornia herbacea* (family Chenopodiaceae) have been shown to activate diverse types of cells of the immune system *in vitro*. A recent study examined the *in vivo* immunostimulatory activity of the polysaccharides isolated from *Salicornia herbacea*. The polysaccharides efficiently induced cytokine production, nitric oxide release, expression of surface molecules

(family Oleaceae) is used in tribal herbal medicine for the treatment of many kinds of acute or chronic inflammatory diseases. The recent phytochemical analysis of *Nyctanthes arboristris* revealed the presence of tertiary alkaloids, represented mainly by 7-(alpha-anilino-p-nitrobenzyl)-8-quinolinol and quaternary alkaloids, belonging to protoberberines and aporphines\textsuperscript{[31]}. These substances may influence the immuno-bioactivities of *Nyctanthes arboristris*. An ethanolic extract of *Nyctanthes arboristris* (NAEE) was screened in rats for humoral and cell-mediated immune responses. Oral administration of the NAEE to rats at 50, 100, 150 and 200 mg/kg significantly enhanced the circulating antibody titer when challenged with SRBCs and heat-killed *Salmonella* antigens. The chronic administration of NAEE increased the total counts of WBCs and potentiated the DTH reactions. The present study confirmed the strong immuno-bioactivities in the extracts of *Nyctanthes arboristris*\textsuperscript{[41]}. A 29 *Ocimum sanctum* *Ocimum sanctum* commonly known as “Tulsi” has been extensively used in Ayurvedic system of medicine for various ailments and has been shown to possess significant adaptogenic or anti-stress properties\textsuperscript{[42]}. A steam distilled extract of *Ocimum santum* leaves has been shown to enhance anti-SRBCs and IgE antibody titer and to reduce antigen-induced histamine released from peritoneal mast cells\textsuperscript{[43]}. An attempt has also been made to explore the possible mechanism of its immunostimulatory activity. *Ocimum sanctum* extract produced a significant increase in anti-SRBCs antibody titer and a decrease in percentage histamine released from the peritoneal mast cells of sensitized rats (humoral immune responses), and decreases in footpad thickness and percentage leucocyte migration inhibition (LMI) (cell-mediated immune responses). *Ocimum sanctum* appeared to modulate both humoral and cell-mediated immune responsiveness and these immunostimulatory effects may be mediated by GABAergic pathways\textsuperscript{[45]}. A 30 *Panax ginseng* *Panax ginseng* (family Araliaceae) is a Korean plant which is widely used as a general health tonic. Ginsan, a *Panax ginseng* polysaccharide that contains glucopyranoside and fructofuranoside, has immunostimulatory effects. Since its initial purification, ginsan has been shown to have critical effects on immune cells\textsuperscript{[44]}. As an immunostimulator, ginsan played a radio-protective role in hematopoietic and immune cells. It increased the number of bone marrow cells, splenocytes, and some hematopoietic stem cells and enhanced the production of cytokines involved in hematopoietic recovery. Therefore, ginsan appeared to protect the host from ionizing radiation via its immunostimulatory activities\textsuperscript{[45]}. A 31 *Picrorhiza kurroa* *Picrorhiza kurroa* has been reported to be a promising immunostimulatory
and phagocytic activity in a dose-dependent manner, when added to cultures of a mouse monocytic cell line, RAW 264.7 cells. *In vivo* efficacy was examined in mice implanted with tumor cells, and also in mice immunized with ovalbumin (OVA). It has found that the polysaccharides enhanced the antitumor immune responses in mice implanted with sarcoma-180 cells. In addition, it has also found that the polysaccharides induced strong OVA-specific cytotoxic T-lymphocyte responses in mice. Thus the results confirmed that the polysaccharide purified from *Salicornia herbacea* exerted immunostimulatory activity in vivo.[75]

**1.35 Tinospora cordifolia** *Tinospora cordifolia* is a large, glabrous and deciduous climbing shrub belonging to the family Menispermaceae. This plant is reported to benefit the immune system in a variety of ways.[76] The alcoholic and aqueous extracts of *Tinospora cordifolia* have been tested successfully for immunostimulatory activity. It helped increasing the effectiveness of WBC and building up the body’s immune system. TC-1 (cerodane furanoditerpeno glycoside), TC-2 (cordioside), TC-4 (syringin), TC-5 (cordifolioside A), TC-6 (cordifolioside B) and TC-7 (cordol) isolated from *Tinospora cordifolia* were found to have anticomplement and immunostimulating activities. TC-4 and TC-7 inhibited the *in vitro* immunohaemolysis of antibody-coated sheep erythrocytes by guinea pig serum. The reduced immunohaemolysis was found to be due to the inhibition of the C3-convertase of the classical complement pathway. The compounds also gave rise to a significant increase in IgG antibodies in serum. Both humoral immunity and cell-mediated immunity were also dose-dependently enhanced. Macrophage activation was reported for TC-2, TC-5 and TC-7 and this activation was more pronounced with increasing incubation times.[77]

**1.36 Tridax procumbens** *Tridax procumbens* (family Compositae) has been extensively used in Ayurvedic system of medicine for various ailments. Earlier studies on the extracts of *Tridax procumbens* revealed remarkable immunostimulatory activity of the *Tridax procumbens* ethanol-insoluble fraction extract. The *in vitro* (phagocytosis) and *in vivo* (haemagglutination and DTH) tests were used to study the effect of the extract and fractions on the cellular and humoral immunity. Alcoholic extract revealed significant immunostimulation by *in vitro* phagocytosis, DTH and haemagglutination model. Oral administration of ethyl acetate fraction and n-butanol fraction among the four fractions (20 to 40 mg/kg) significantly inhibited SRBCs-induced DTH reactions and significantly increased the *in vitro* phagocytic index. It also produced a significantly, dose-related decrease in sheep erythrocyte-specific haemagglutination antibody titer. The results obtained indicated the ability of the flavonoidal fraction and saponin fraction of *Tridax procumbens* to modulate both the cell-mediated and the humoral components of the immune system and explored the phytoconstituents responsible for immunomodulatory potential from *Tridax procumbens*.[78]

**1.37 Withania somnifera** *Withania somnifera* has been an important herb in the Ayurvedic and indigenous medical systems for over 3000 years. It is a small, woody shrub of the Solanaceae family.[79] Administration of an extract from the powdered roots of the plant *Withania somnifera* was found to stimulate immunological activity in BALB/c mice. Treatment with five doses of *Withania somnifera* root extract was found to enhance the total WBC count on the 10th day. Bone marrow cellularity as well as α-esterase-positive cell number also increased significantly after the administration of the extract. Treatment with the extract along with the antigen (SRBC) produced enhancements in the circulating antibody titer and the number of PFC in the spleen. Maximum number of PFC (985 PFC/10⁶ spleen cells) was obtained on the 4th day. *Withania somnifera* extract inhibited DTH reaction in mice (Mantoux test). Administration of *Withania somnifera* extract also showed an enhancement in phagocytic activity of peritoneal macrophages (76.5 pigmented cells/200) compared with the control (31.5 pigmented cells/200) in mice. These results confirmed the immunomodulatory activity of *Withania somnifera* extract, which is a known immunomodulator in indigenous medicine.[80, 81]

**2 Conclusion**

Immunostimulant drugs are agents that could enhance the body’s resistance against infections. These drugs are most commonly used in autoimmune diseases, allergic conditions, cancers, acquired immune deficiency syndrome, viral infections, etc. Modern medical healthcare in developing countries such as India is still a far reaching goal due to economic constraints. Only a few plants have been screened for immunostimulatory activities. From the above review, it is evident that there are several medicinal plants which have immunostimulatory activity (Table 1) but inadequate evidence does not allow their use in clinical practice. Therefore, immunostimulators seems to be valuable in the future research of herbal medicine.
Table 1  Summary of immunostimulatory plants reviewed

<table>
<thead>
<tr>
<th>No.</th>
<th>Plant name</th>
<th>Part used</th>
<th>Extract/Phytoconstituents</th>
<th>Mode used</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Actinidia macroperma</td>
<td>Fruit</td>
<td>Aqueous</td>
<td>Lymphocyte proliferation, natural killer cell cytotoxicity, phagocytic activity</td>
</tr>
<tr>
<td>2</td>
<td>Aesculus indica</td>
<td>Leaves</td>
<td>Aqueous, alcoholic</td>
<td>Neutrophil adhesion test, delayed type hypersensitivity response</td>
</tr>
<tr>
<td>3</td>
<td>Allium sativum</td>
<td>Bulb</td>
<td>Proteins</td>
<td>Contact hypersensitivity test</td>
</tr>
<tr>
<td>4</td>
<td>Aloe vera</td>
<td>Gel</td>
<td>Aqueous</td>
<td>Macrophage activation</td>
</tr>
<tr>
<td>5</td>
<td>Andrographis paniculata</td>
<td>Leaves</td>
<td>Ethanolic</td>
<td>Delayed type hypersensitivity response</td>
</tr>
<tr>
<td>6</td>
<td>Asparagus racemosus</td>
<td>Roots</td>
<td>Alcoholic</td>
<td>Sepsis induction test</td>
</tr>
<tr>
<td>7</td>
<td>Azadirachta indica</td>
<td>Leaves</td>
<td>Aqueous</td>
<td>Delayed type hypersensitivity response</td>
</tr>
<tr>
<td>8</td>
<td>Baliospermum montanum</td>
<td>Roots</td>
<td>Aqueous</td>
<td>Neutrophil phagocytic test</td>
</tr>
<tr>
<td>9</td>
<td>Boerhaavia diffusa</td>
<td>Roots</td>
<td>Aqueous</td>
<td>Delayed type hypersensitivity response</td>
</tr>
<tr>
<td>10</td>
<td>Bouwelia carterii</td>
<td>Bark</td>
<td>Triterpenoids</td>
<td>T-lymphocyte proliferation</td>
</tr>
<tr>
<td>11</td>
<td>Capparis seyalanca</td>
<td>Leaves</td>
<td>Ethanolic</td>
<td>Neutrophil adhesion test, delayed type hypersensitivity response</td>
</tr>
<tr>
<td>12</td>
<td>Caesalpinia bonducella</td>
<td>Seed</td>
<td>Ethanolic</td>
<td>Neutrophil adhesion test, delayed type hypersensitivity response, carbon clearance test</td>
</tr>
<tr>
<td>13</td>
<td>Centella asiatica</td>
<td>Leaves</td>
<td>Ethanolic</td>
<td>Delayed type hypersensitivity response, reticuloendothelial stimulating test, phagocytosis</td>
</tr>
<tr>
<td>14</td>
<td>Chlorella vulgaris</td>
<td>Whole part</td>
<td>Protein hydrolysate</td>
<td>Delayed type hypersensitivity response</td>
</tr>
<tr>
<td>15</td>
<td>Chlorophytum borivitianum</td>
<td>Roots</td>
<td>Ethanolic</td>
<td>Neutrophil adhesion test, delayed type hypersensitivity response, carbon clearance test</td>
</tr>
<tr>
<td>16</td>
<td>Clerodendrum phomoidis</td>
<td>Roots</td>
<td>Methanolic</td>
<td>Delayed type hypersensitivity response, carbon clearance test</td>
</tr>
<tr>
<td>17</td>
<td>Curcailgo orchidoides</td>
<td>Roots</td>
<td>Methanolic</td>
<td>Delayed type hypersensitivity response, plaque-forming test, macrophage migration index</td>
</tr>
<tr>
<td>18</td>
<td>Curcuma longa</td>
<td>Rhizome</td>
<td>Curcumin</td>
<td>Conocalavin A-induced proliferation test</td>
</tr>
<tr>
<td>19</td>
<td>Eclipta alba</td>
<td>Whole plant</td>
<td>Edalbatin</td>
<td>Carbon clearance test, cyclophosphamide-induced immunosuppression test</td>
</tr>
<tr>
<td>20</td>
<td>Emblica officinalis</td>
<td>Fruit</td>
<td>Ethanolic</td>
<td>Rat splenocyte test</td>
</tr>
<tr>
<td>21</td>
<td>Epilobium angustifolium</td>
<td>Whole plant</td>
<td>Oenothein B</td>
<td>Phagocyte activation</td>
</tr>
<tr>
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<td>Ficus benghalensis</td>
<td>Root</td>
<td>Aqueous</td>
<td>Delayed type hypersensitivity response</td>
</tr>
<tr>
<td>23</td>
<td>Gymnema sylvestre</td>
<td>Leaves</td>
<td>Aqueous</td>
<td>Nitroblue tetrazolium test, neutrophil locomotion test</td>
</tr>
<tr>
<td>24</td>
<td>Heracleum nepalense</td>
<td>Roots</td>
<td>Quercetin glycoside</td>
<td>Delayed type hypersensitivity response, carbon clearance test</td>
</tr>
<tr>
<td>25</td>
<td>Janakia arayalpathra</td>
<td>Roots</td>
<td>Extract</td>
<td>Delayed type hypersensitivity response</td>
</tr>
<tr>
<td>26</td>
<td>Mangifera indica</td>
<td>Bark</td>
<td>Alcoholic</td>
<td>Activation of T and B cells</td>
</tr>
<tr>
<td>27</td>
<td>Morinda citrifolia</td>
<td>Fruit</td>
<td>Hydroalcohol</td>
<td>Phagocytosis</td>
</tr>
<tr>
<td>28</td>
<td>Nyctanthes arbor tristis</td>
<td>Fruit</td>
<td>Ethanolic</td>
<td>Delayed type hypersensitivity response</td>
</tr>
<tr>
<td>29</td>
<td>Ocimum sanctum</td>
<td>Leave</td>
<td>Steam distilled extract</td>
<td>Delayed type hypersensitivity response</td>
</tr>
<tr>
<td>30</td>
<td>Panax ginseng</td>
<td>Roots</td>
<td>Polysaccharide</td>
<td>Increases number of bone marrow cells, splenocytes, and hematopoietic stem cells and cytokines production</td>
</tr>
<tr>
<td>31</td>
<td>Pterocarya kurra</td>
<td>Leaves</td>
<td>Ethanolic</td>
<td>Delayed type hypersensitivity response</td>
</tr>
<tr>
<td>32</td>
<td>Piper longum</td>
<td>Fruit</td>
<td>Alcoholic</td>
<td>Increases total white blood cell count</td>
</tr>
<tr>
<td>33</td>
<td>Randia dumetorum</td>
<td>Fruit</td>
<td>Methanol</td>
<td>Delayed type hypersensitivity response, cyclophosphamide-induced mycosuppression</td>
</tr>
<tr>
<td>34</td>
<td>Salicornia herbacea</td>
<td>Whole plant</td>
<td>Polysaccharides</td>
<td>Cytokine production, phagocytic activity</td>
</tr>
<tr>
<td>35</td>
<td>Timospora cordifolia</td>
<td>Fruit</td>
<td>Alcoholic</td>
<td>Delayed type hypersensitivity response</td>
</tr>
<tr>
<td>36</td>
<td>Tridax procumbens</td>
<td>Aerial parts</td>
<td>Ethanolic</td>
<td>Delayed type hypersensitivity response</td>
</tr>
<tr>
<td>37</td>
<td>Witthania somnifera</td>
<td>Roots</td>
<td>Extracts</td>
<td>Delayed type hypersensitivity response</td>
</tr>
</tbody>
</table>

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具有免疫刺激活性的药用植物概览

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摘要：人类使用药用植物治疗疾病可以追溯到远古时代。如今仍有很多人依赖传统医药进行日常保健。印度阿育吠陀医学及其他印度的古老文献中记载了多种植物的药用功效。这些药用植物中，有很多被认为能够提高人体对于外界感染的自然抵抗力，即很多药用植物具有免疫刺激活性。本文对这些具有免疫刺激活性的药用植物进行了综述。

关键词：佐剂，免疫；植物，药用；综述