WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 9, 172-188. Review Article ISSN 2277– 7105

GENERAL OVERVIEW ON IMMUNOMODULATOR ACTIVITY OF HERBAL NATURAL PRODUCTS

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Article Received on
01 July 2020,

Revised on 21 July 2020,
Accepted on 11 August 2020,

DOI: 10.20959/wjpr20209-17918

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ABSTRACT

Herbal immunomodulator is a substance which stimulates or suppresses the components of immune system including both innate and adaptive immune responses. A various medicinal plant products modulates immune system has become subject for scientific investigations currently wordwide. Many plants and phytoconstitutents are responsible for immunomodulation have been explained. A number of plant based principles can be isolated with potential immunomodulator activity that can be explained and justified as use in traditional medicine in the past and can form the basis for further research in the future as well. Some of these plants are, Allium sativum, Morus alba, Acacia catechu, Tinospora cordifolia, and Mangifera indica. The aim of this review is to highlight results of research done on immunomodulators of plant origin. The selection of paper was made using more relevant database for the biomedical science on the basis of their pharmacological use. The review also discusses biological screening methods for various plant drugs that focus on revealing the mechanism involved in immunomodulation.

KEYWORDS: Medicinal Plants, Immunomodulators, Traditional medicine, Plant extracts.

INTRODUCTION

Modulaton of immune functions using medicinal plants and their products as a possible therapeutics measures has become an acepted therapeutic approach. Immunity is a homeostatic process, a series of delicated balanced complex, multicellular and physiologic mechanisms that allow an individual to distinguish foreign material from self and neutralize or eliminate the foreign matter.[1]

Immunomodulators

These are biological or synthetic substances that can stimulate, suppress, or modulate the immune system including both adaptive and innate immunity.[2]

Classification of immunomodulators: Basically, immunomodulator can be classified into following three categories:

Immunostimulants: The term immunostimulation comprise a prophylactic or therapeutic concept which aims at the stimulation of our nonspecific immune system. This implies primarily the non antigen dependent stimulation of the function and efficiency of granulocytes, macrophages, complement and natural killer (NK) cells.[1] Are nonspecific has they investigated as enhancements to body resistance to infection. they can act on both adaptive and innanate immune responses.[2]

Mechanism of Immuno-stimulation: Immunological defense is a complicated interplay between nonspecific and specific, cellular and humoral immune responses, stimulation and suppression of immunocompetent cells, and the influence of endocrine and other mechanisms upon the immune system. Primary targets of the Immunostimulant are T or B lymphocytes or the complement system, an increase in phagocytosis by macrophages and granulocytes plays a central role in immunostimulation. Activation of macrophages is probably important for the stimulating agents to remain in contact with the reactive cell. The second most important role is the stimulation of T lymphocytes, which can be achieved either directly or indirectly, via macrophages.[1]

Immunosuppressants

Are a structurally and functionally heterogenous group of drugs used to treat different types of organ transplant rejection and autoimmuno diseases, graft rejection, graft versus host diseases, hypersensitivity immune reaction (immediate or delayed type) immune pathology associated with infections.[2]

Clinically application of immunosuppresants are as follows

1) To suppress rejection of transplanted organs and tissues (kidney, bone marrow, heart, liver etc)

2) To suppress graft-versus-host disease (i.e. response of lymphocytes in the graft to host antigens) in bone marrow transplants.

3) To treat a variety of conditions, which, while not completely understood, are believed to have an important autoimmune component in their pathogenesis i.e. myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis, psoriasis and ulcerative colitis.
4) Selective immunosuppression for prevention of Rh hemolytic disease of the newborn.

Side Effects of Immunomodulator Drugs

There are various side effects are associated with the use of these drugs i.e. Pulmonary toxicity, Myelosuppression, Alopecia, Increased risk of infection, Hepatic fibrosis, Lymphoma (Epstein–Barr virus associated), Nephrotoxicity, neurotoxicity (tremor, headache, motor disturbances and seizures), GI complaints, hypertension, hyperkalemia, hyperglycemia, and diabetes, Renal dysfunction, tremor, hirsutism, hypertension, hyperlipidemia, gum hyperplasia, hyperuricemia, hyper cholesterolemia, nephrotoxicity, hypertension, diabetogenic, Elevated LDL cholesterol etc.

Immunomodulation by Medicinal Plants

Plant extracts used in traditional therapy are being reviewed for their chemo protective and Immunomodulatory activities. Immunomodulators are biological response modifiers; exert their antitumor effects by improving host defense mechanisms against the tumor. They have a direct anti-proliferative effect on tumour cells and also enhance the ability of the host to tolerate damage by toxic chemicals that may be used to destroy cancer.

Immunomodulatory therapy could provide an alternative to conventional chemotherapy for a variety of diseased conditions, especially when host‟s defense mechanisms have to be activated under the conditions of impaired immune responsiveness or when a selective immunosuppression has to be induced in a situation, like inflammatory diseases, auto-immune disorders ad organ/bone marrow transplantation.Some of these planta *are Withania somnifera, Tinospora cordifolia, and Mangifera indica.* A lot more are still to be explored and offer scope for further investigation.[1]

Table 1: A brief description of common plant derived immunomodulators.[2]

Botonical Name /Family	Common Name	Part Used	Chemical Constitutents	Other Biological Activities
Ganoderma lucidum (Fr.) P. Karst. (Polyporaceae	Reishi mushroom	Whole plant	Flavonoids, triterpenes	Antioxidant
Nyctanthes arbor-tristis L. (Oleaceae)	Paarijaata	Leaf, seeds	Iridoid glucosides	Anti-inflammatory, antispasmodic

Actinidia macrosperma C. F. Liang (Actinidiaceae	Actinidia	Fruits	Alkaloids, saponins	Antileprotic
Acacia catechu Willd. (Leguminosae	Khadira	Leaf	Flavonoids, quercetin	Hypoglycaemic, astringen
Boswellia spp. (Burseraceae)	Shallaki	Gum resin	Triterpenes, ursanes	Hypoglycaemic.
Hibiscus rosa sinensis Linn. (Malvaceae)	Japaa	Flowers	Cyclopropanoids	Antidiarrheal, anti-inflammatory
Cleome gynandra Linn. (Capperdiceae)	Tilaparni	Leaf, seeds, rots	Hexacosanol, kaempferol	Anti-inflammatory.
Hyptis suaveolens (L.) Poit. (Lamaceae)	Tumbaaka	Leaf, flowers	Lupeol, beta-sitosterol	Carminative, antispasmodic
Citrus natsudaidai Hayata (Rutaceae)	Japanese summer grape fruit	Fruits	Auraptene, flavonoids	Antioxidant
Allium hirtifolium Boiss. (Alliaceae)	Persian shallot	Herb	Thiosulfinates, flavonoids	Antirheumatic, anti-inflammatory.
Randia dumetorum Lamk. (Rubiaceae)	Madana	Fruits	Saponins, triterpenes	Chlorosis, antiarthritic
Acanthopanax sessiliflorus (Rupr. & Maxim.) (Araliaceae)	Prickly spine	Shoots and roots	Biopolymers	Lympho-proliferative activity
Agelas mauritianus (Porifera	Agelas	Sponge	Glycolipid (a-galactosylceramide.	Phagocytotic activity.
Artemisia annua Linn. (Compositea)	Wormwood	Herb	Artemisinin	Immunosuppressive
Genus Aristolochia (Aristolochiaceae)	Pipevine	Leaves	Aristolochic acid	Antiangiogenic, employed in prostate cancer.
Calendula Officinalis L. (Asteraceae)	Garden Marigold	Flowers	Polysaccharides, proteins, fatty acids, carotenoids, flavonoids, triterpenoids	Antitumor antiviral activity, anti-HIV properties
Camellia sinensis L. (Theaceae)	Tea	Leaves	_)Epigallocatechin gallate, quercetin, gallicacid	Anticancer activity, lipid lowering activity, anticataract activity, hepatoprotective and antioxidant.6
Cannabis sativa (Cannabaceae)	Common hemp	Leaves	Cannabinoids	Immunomodulatory
Centella asiatica Linn. (Umbelliferae),	Brahmi	Herb	Triterpenoid saponins	Immunomodulator
Carpobrotus edulis L. (Aizoaceae)	Fig Marigold	Flowers, fruit	Alkaloids	Immunomodulator
a occidentalis L. (Arborvitae)	White cedar	Leaves	Polysaccharides	Immunomodulator

Eclipta alba L. (Compositae)	Bringraja	Leaves	Triterpenoid glucoside	Anticancer, antileprotic, analgesic, antioxidant, antimyotoxic
Euphorbia hirta linn. (Euphorbiaceae	Asthma weed	Herb	Quercitol, myricitrin, gallic acid	Anti-inflammatory activity, sedative and anxiolytic activity. Brain tonic.
Thuja occidentalis L. (Arborvitae)	White cedar	Leaves	Polysaccharides	Immunomodulator
Viscum album L. (Loranthaceae)	Mistletoe	Leaves and young twigs, berries	Viscotoxins, polyphenols, polysaccharides	Antitumoral effect
Larrea divaricata DC. (Zygophyllaceae)	Creosote Bush	Herb	Lignans	Anti-inflammatory.
Lycium barbarum Linn. (Solanaceae)	-	Fruits	Polysaccharide-protein complexes	Antioxidant.
Matricaria chamomilla (Rhabdoviridae)	Chamomile	Protein	Immunomodulator	
Moringa oleifera L. (Moringaceae)	Sahijan	Leaves	Vitamin A, B, C, carotenoids, saponins	Antioxidant
Pestalotiopsis leucothes (Amphisphaeriaceae	-	Fungus	Terpenes	Immunomodulator
Rhodiola imbricate Gray. (Crassulaceae	Roseroot	Rhizomes	Phenolics	Immunostimulating properties
Salicornia herbacea (Chenopodiaceae)	Glasswort	Herb	Polysaccharides	Immunomodulator
I Ocimum sanctum Linn. (Labiateae	Tulasi	Entire plant	Essential oils such as eugenol, cavacrol, derivatives of ursolic acid, apigenin	Carminative, stomachic, antispasmodic, antiasthmatic, hepatoprotective
Morus alba Linn. (Moraceae)	Brahmdaru	Fruits, leaves, bark	Flavonoids, anthocyanins	Expectorant, hypocholesterolaemic, Diuretic
Panax ginseng Wall. (Araliaceae)	Ninjin	Fruits, root	Saponins such as ginsenosides, panaxdiol, panaxtriole and oleanolic	Adaptogenic properties, antiarrhythmic
Achillea millefolium C. Koch (Compositae	Yarrow	Leaves	Flavonoids, alkaloids, polyacetylenes, coumarins, triterpenes	Anti-inflammatory, antispasmodic, antipyretic, diuretic
Andrographis paniculata Nees (Acanthaceae)	Kaalmegha	Leaves	Diterpenes	Hepatoprotective, antispasmodic, blood purifier, febrifuge
Asparagus racemosus Wild. (Liliaceae)	Shatavaari	Roots	Saponins, sitosterols	Ulcer healing agent, nervine tonic, antigout.

Picrorhiza scrophulariiflora Benth. (Scrophulariaceae	Kutki	Roots	Iridoid glycosides, amphicoside	Antioxidant
Gymnema sylvestre R.Br. (Asclepiadaceae	Gurmaar	Leaves	Sapogenins	Antidiabetic, diuretic, antibilious
Terminalia arjuna Roxb. (Combretaceae	Arjuna	Leaves, bark	Flavonoids, oligomeric proanthocyanidins, tannins	Cardiotonic, diuretic, prescribed for hypertension

Herbal Plants as Immunomodulator

Morus alba (Mulberry)

Methanolic extract of *Morus alba* was administered orally at low dose and high dose of 100 mg/kg and 1 g/kg respectively and Ocimum sanctum (100 mg/kg, po) was used as standard drug. It showed significant increase in the phagocytic index in carbon clearance assay, a significant protection against cyclophosphamide induced neutropenia and increased the adhesion of neutrophils in the neutrophil adhesion test. Hence, it was concluded that Morus alba increases both humoral immunity and cell mediated immunity.[3]

Withania sonifera

Administration of an extract from the powdered root of the plant *Withania somnifera* was found to stimulate immunological activity in mice. Treatment with five doses of Withania root extract (20 mg/dose/animal; i.p.) was found to enhance the total WBC count (17125 cells/mm (3)) on 10th day. Bone marrow cellularity (27x10(6) cells/femur) as well as alpha-esterase positive cell number (1800/4000 cells) also increased significantly ($P<0.001$) after the administration of Withania extract. Treatment with Withania extract along with the antigen (SRBC) produced an enhancement in the circulating antibody titre and the number of plaque forming cells (PFC) in the spleen. Maximum number of PFC (985 PFC/10(6) spleen cells) was obtained on the fourth day. Withania extract inhibited delayed type hypersentivity reaction in mice (Mantoux test). Administration of Withania extract also showed an enhancement in phagocytic activity of peritoneal macrophages (76.5 pigmented cells/200) when compared to control (31.5/200 cells) in mice. These results confirm the immunomodulatory activity of W. somnifera extract, which is a known immunomodulator in indigenous medicine.[4]

Sophora subprosrate

The results showed that SSP1 stimulated proliferation and IFN-gamma secretion of murine splenic lymphocytes at concentrations of 50, 100, 200 or 400 mg/L in vitro. SSP1 increased the levels of interleukin-6 and tumor necrosis factor-alpha in immunosuppressed mice induced by subcutaneous injection of dexamethasone at 1.25 mg/kg. Administration of SSP1 by intraperitoneal injection significantly raised spleen index, glutathione level, glutathione peroxidase activity and lysozyme activity in the immunosuppressed mice.[5]

Jatropha curcas

The immunomodulatory effect of an 80% aqueous methanol extract (AME) and compounds 1-5 (0.25 mg/kg body wt) to one-day-old specific pathogen-free (SPF) chicks was determined. Stimulation of both humoral and cell-mediated seroresponse was observed. Remarkable effective increases of the antibody titers, lymphocyte and macrophage cells, in blood were recorded.[6]

Acacia catechu

Acacia catechu extract showed an increase in the neutrophil adhesion to the nylon fibres, produced a significant increase in the phagocytic index and a significant protection against cyclophosphamide induced neutropenia indicating its effect on cell mediated immunity. On the other hand, Acacia catechu extract produced a significant increase in the serum immunoglobulin levels, increase in the haemagglutination titre values and decreased the mortality ratio in mice, suggesting its effect on the humoral arm of the immune system. From the above results, it was concluded that the aqueous extract of Acacia catechu has a significant effect on both cell mediated and humoral immunity.[7]

Picrorrhiza Scrophulariiflora

One glycoside (scrocaffeside A,) from the methanol extract of *Picrorhiza scrophulariiflora*, shows immunomodulatory properties by structure. The scrocaffeside A enhanced proliferation of splenocytes and their response to polyclonal T cell mitogen concanavalin A (Con A) and lipopolysaccharide (LPS). There was also a significant increase in the activity of peritoneal macrophages and natural killer cell when treated with doses of scrocaffeside A between 5 microg/ml and 125 microg/ml. A dose-dependent increase was also observed in the populations of mature T cell subsets. The production of cytokines and the CD4/CD8 population of splenocytes were also elevated. The levels of interleukin (IL)-2, IL-4, IL-12, and (IFN)-gamma expressed by cultured splenocytes were significantly increased when the

cells were exposed to scrocaffeside A. These results indicate that scrocaffeside A may exert immunoenhancement effects on immune system. In addition to its traditional use in some diseases, it may become a new immunostimulating agent in the future.[8]

Planago asiatica

The seeds of *Plantago asiatica* L. were often used as a traditional Chinese medicine for some immunologically weak patients suffering from chronic illness. These uses could be related to immunomodulatory properties of the plant. AIM OF THE STUDY: In this study, effects of extract of the seeds of Plantago asiatica L. (ES-PL) were investigated on the maturation of dendritic cells (DCs), which play significant role in primary immune system.[9]

Panax ginseng

Ginseng is believed to have beneficial effects against human diseases, and its active components, ginsenosides, may play critical roles in its diverse physiological actions. However, the mechanisms underlying ginseng's effects remain to be investigated. We hypothesize some biological effects of ginseng are due to its anti-inflammatory effects. Seventy percent ethanol-water extracts of ginseng significantly inhibited the transcription and secretion of CXCL-10 following TNF-alpha stimulation. Nine ginsenosides including Rb1, Rb2, Rc, Rd, Re, Rf, Rg1, Rg3 and Rh1 were identified in our extract by HPLC. Seven out of nine ginsenosides could significantly inhibit TNF-alpha-induced CXCL-10 expression in U937 cells and give comparable inhibition of CXCL-10 transcription to those with the extract. However, the CXCL-10 suppressive effect of individual ginsenosides was less than that of the crude extract or the mixture of ginsenosides.[10]

Caesalpinia bonducella

The evaluation of immunomodulatory potential by oral administration of ethanolic seed extract of *Caesalpinia bonducella* (200-500 mg/kg) evoked a significant increase in percent neutrophil adhesion to nylon fibers as well as a dose-dependent increase in antibody titre values, and potentiated the delayed-type hypersensitivity reaction induced by sheep red blood cells. Also it prevented myelosuppression in cyclophosphamide drug treated rats and good response towards phagocytosis in carbon clearance assay.[11]

Garlic (Allium sativum)

Garlic (Allium sativum), an important medicinal spice, displays a plethora of biological effects including immunomodulation. Although some immunomodulatory proteins from

garlic have been described, their identities are still unknown. The present study was envisaged to isolate immunomodulatory proteins from raw garlic, and examine their effects on certain cells of the immune system (lymphocytes, mast cells, and basophils) in relation to mitogenicity and hypersensitivity.[12]

Cynodon dactylon

Fresh juice of the grass was prepared as indicated for use in traditional medicine and standardized for solid content. Its total phenol content was estimated by Folin-Ciocalteau method. Freshly prepared juice was investigated for its effect on doxorubicin-induced DNA damage in vitro. Its immunomodulatory activity was tested on balb/c mice by the humoral antibody response which was determined by haemagglutination antibody titer and spleen cell assay.[13]

Terminalia arjuna

Terminalia arjuna back powder (400 mg/kg, po) significantly reduced formalin-indued paw oedema at 24 h but not carrageenan-induced paw oedema. It significantly increased the anti-SRBC antibody titre in the secondary phase of immune response. The same dose significantly reduced the duration of licks and bites in both phases of formalin-induced pain response and showed significant increase in tail flick latency at higher dose (800 mg/kg, po). These effects of T. arjuna were antagonised by pretreatment with naloxone (1 mg/kg, ip). These findings support the hypothesis that T. arjuna has anti-inflammatory potential against some phlogistic agents along with some immunomodulatory activity and also has antinococeptive action probably mediated via central opioid receptors.[14]

Schisandra arisanensis

An acetone extract of the fruits of the Taiwanese medicinal plant Schisandra arisanensis has yielded 11 new oxygenated lignans. Four of these, named arisantetralones A-D (1-4), possess the aryltetralone skeleton, while the other seven, named arisanschinins F-L (5-11), are polyoxygenated C(18)-dibenzocyclooctadiene lignans.[15]

Rhus toxicodendron(rhus tox)

Toxicodendron pubescens is a botanical name of *Rhus toxicodendron* (Rhus tox). This plant is widely used in its homeopathically diluted form in the treatment of inflammatory and edematous conditions.[16]

Pteridium aquilinum (bracken fern)

Pteridium aquilinum (bracken fern) is one of the most common plants. The overall objective of this study was to evaluate the immunomodulatory effects of bracken fern following daily ingestion of its extract by a murine host over a period of 14 (or up to 30) days. In C57BL/6 mice administered (by gavage) the extract, histological analyses revealed a significant reduction in splenic white pulp area. Among a variety of immune response parameters/functions assessed in these hosts and isolated cells, both delayed-type hypersensitivity (DTH) analysis and evaluation of IFN gamma production by NK cells during T(H)1 priming were also reduced.[17]

Boerhaava diffusa

The effect of Punarnavine on the immune system was studied using Balb/c mice. Intraperitoneal administration of Punarnavine (40 mg/kg body weight) was found to enhance the total WBC count on 6(th) day. Bone marrow cellularity and number of alpha-esterase positive cells were also increased by the administration of Punarnavine. Treatment of Punarnavine along with the antigen, sheep red blood cells (SRBC), produced an enhancement in the circulating antibody titer and the number of plaque forming cells (PFC) in the spleen. Maximum number of PFC was obtained on the 6(th) day. Punarnavine also showed enhanced proliferation of splenocytes, thymocytes and bone marrow cells both in the presence and absence of specific mitogens in vitro and in vivo.[18]

Dioscorea japonica

The aim of this study was to elucidate the effect of the major storage protein dioscorin isolated from two different yam species, Tainong No. 1 (TN1-dioscorins) and Japanese yam (Dj-dioscorins), on the immune activities of mice. Dj-dioscorins, like TN1-dioscorins, could induce expression of the pro-inflammatory cytokines and stimulate phagocytosis of RAW 264.7. Intraperitoneal injection of the TN1-dioscorins into mice stimulated phagocytosis of bone marrow, spleen, and thymic cells. In contrast, the T and B cells in bone marrow, spleen, and thymus isolated from mice injected with Dj-dioscorins had higher proliferative responses to mitogens. Furthermore, Dj-dioscorins enhanced proliferation of CD4(+), CD8(+), and Tim3(+) (Th1) cells in spleen and CD19(+) cells in both spleen and thymus. Supplement of Dj-dioscorins in the lymphoid cells isolated from Dj-dioscorins primed mice induced cell proliferation of both spleen and thymic cells.[19]

Andographis paniculata

The immunomodulatory activity of HN-02, an extract containing a mixture of andrographolides (i.e., andrographolide [88 +/- 5%] plus 14-deoxyandrographolide and 14-deoxy-11,12-didehydroandrographolide together [12 +/- 3%]) 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.[20]

Curcuma longa

Curcumin is a polyphenol derived from the dietary spice turmeric. It has been shown to regulate numerous transcription factors, cytokines, adhesion molecules, and enzymes that have been linked to inflammation. In addition to inhibiting the growth of a variety of pathogens, curcumin has been shown to have nematocidal activity. The present study was designed to evaluate the schistosomicidal activity of curcumin in vivo as well as immunomodulation of granulomatous inflammation and liver pathology in acute schistosomiasis mansoni.[21]

Tinospora cordifolia

Immunostimulatory activity was assessed by lymphocyte proliferation and macrophage activation assays. Fresh guduchi stem/leaf, guduchi satwa and guduchi capsules were also analyzed for the presence of guduchi ImP. The confirmation of an immunomodulatory protein in guduchi stem showing lymphoproliferative and macrophage-activating properties reinforces the rationale of the use of guduchi preparations in several Ayurvedic medicines for immunomodulation.[22]

Table 2: Pharmacology of immunomodulator activities from herbal medicinal plants.[2]

Plant /Family name	Dose administered	Type of solvent extract	In vitro in vivo model	Mechanism involved in observation
Ocimum sanctum Linn. (Labiateae	200 mg/kg p.o.	Aqueous/alcoholic	HA titer	Extract shows increased DTH to sheep red blood cells SRBCs. Alcoholic extract was more potent than aqueous in producing delayed type hypersensitivity response. Both extracts have marginal stimulatory effect on humoral

				immunity.12 3 mg/kg, i.p. Seed oil HA titer Oil shows significant immunomodulatory effect, increase in SRBCs antibody titer and a decrease in percentage histamine release from the peritoneal mast cell of sensitized rats (humoral immune responses); also a decrease in footpad thickness and percentage leucocyte migration inhibition (cellmediated immune responses) is observed.
Morus alba Linn. (Moraceae	100 mg/kg, 1 g/kg, p.o.	Methanolic	HA titer, carbon clearance assay, cyclophosphamide induced neutropenia and neutrophil adhesion test	Extract affects humoral immunity as shown in the indirect hemagglutination test, serum immunoglobulin levels and mice lethality test. It also affects cell-mediated immunity, showing significant increase in the neutrophil adhesion, carbon clearance and a reduction in cyclophosphamide induced neutropenia
Panax ginseng Wall. (Araliaceae	100 mg, p.o.	Liquid ginseng extract	Double-blind, placebocontrolled eight-week study	Blood samples collected at baseline and week four. At week eight examined PMN cell chemotaxis, phagocytosis, total lymphocytes, T-helper and T-suppressor cells, and NK-cell activity. Groups

				receiving ginseng experienced consistent improvement in immune system activity at week four and statistically significant differences at week eight, evidenced by improvements in PMN cell chemotaxis, phagocytosis, and total number of T-helper and T-suppressor cells.
Aloe vera Tourn.ex Linn. (Liliaceae)	100 g/mL	Hydrogel	Mouse macrophage cell line, RAW 264.7	Acemannan (primary polysaccharide from Aloe vera gel) incubated on special type of mouse macrophage cell line, RAW 264.7 for 24 h causes immunostimulation due to activation of macrophages
Andrographis paniculata Nees (Acanthaceae	Dose dependent	Alcoholic	Mitogen induced lymphocyte proliferation	Andrographolide acts as inhibitor of TNF-a and induces significant stimulation of both “antigen specific” and “antigen nonspecific” types of immune responses in mice, showing effectiveness against a variety of infectious and oncogenic (cancer causing) agents.
Asparagus racemosus Wild. (Liliaceae)	100 mg/kg body weight	Aqueous	HA titer	Aqueous extract showed immunoadjuvant effect on experimental animals when immunized with diphtheria, tetanus, and pertussis vaccine. Reduced mortality coupled with overall improved

				health status was observed in treated animals, indicating the development of a protective immune response.
Gymnema sylvestre R.Br. (Asclepiadaceae)	25 mg/mL, 50 mg/mL and 100 mg/mL	Aqueous	Neutrophil locomotion and chemotaxis test, phagocytosis of killed Candida albicans and nitroblue terazolium tests	Extract showed significant immunomodulation at all concentrations in various in vitro models by exerting a stimulating effect on phagocytic activity, neutrophil locomotion and chemotaxis.
Terminalia arjuna Roxb. (Combretaceae	400 mg/kg, p.o.	Aqueous, alcoholic	HA titer	Plant showed immunomodulation by increasing the secondary immune response as evidenced by an increase in Anti-SRBC antibody titre (ASRBs) antibody
Hibiscus rosa sinensis Linn. (Malvaceae	75, 150 and 300 mg/ kg, p.o. Hydro alcoholic	Carbon clearance, HA titer and footpad swelling method	Stimulatory effect on both humoral immunity as well as cell mediated immunity by stimulating phagocytosis, increases in DTH	

Many studies have reported the identification of immunomodulatory compounds with pharmacological activity and a limited toxicity. In this context, pharmacology represents the most important way possible to uncover interesting and therapeutically helpful molecules. The phytochemical analysis of plants has revealed a large number of compounds including tannic acid, flavonoids, tocopherol, curcumin, ascorbate, carotenoids, polyphenols, etc., which have been shown to have potent immunomodulatory properties. The herbal mixture preparations of Indian traditional medicine may stimulate immunomodulation due to their content of plants with immunomodulatory properties that probably act synergistically. This

hypothesis along with the lack of toxicity can be important to understand their use in the past as well as currently. From the above review it should be evident that there are many medicinal plants which exert immunomodulatory activity in experimental models at a particular dose. Different types of screening methods both in vivo and in vitro have been employed to determine their pharmacological activity. Some medicinal plants may stimulate the immune system, (e.g., Panax ginseng, Ocimum sanctum, Tinospora cordifolia, and Terminalia arjuna), and some may suppress the immune response (Alternanthera tenella). Also, various secondary metabolites (e.g., alkaloids, glycosides, saponins, flavonoids, coumarins, and sterols) exhibit a wide range of immunomodulating activity. Thus a successful review has been achieved by our above survey.[2]

CONCLUSION

The use of various plant extracts and herbal fed additives in specific dose during the scheduled vaccination regimen may be helpful in obtaining higher protective antibody against different infections including production and development of more effective cell mediate immune response for protection against various bacterial, viral and other diseases. Herbal formulation may be therefore recommended for use as positive immunomodulator. There are several botanical products with potential therapeutic applications because of their high efficacy, low cost and low toxicity.

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