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REVIEW
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Current Status of Indian Medicinal Plants with Immunomodulatory Potential: A Review

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ABSTRACT

Every country in the world has lists of herbal remedies for the treatment of diseases and different other unwanted conditions in humans. Ayurveda is one of the traditional systems of medicine practiced in India and Sri Lanka and can be traced back to 6000 B.C. Modulation of immune responses to alleviate the diseases has been of interest for many years and the concept of 'Rasayana' in Ayurveda is based on related principles. Rasayana is helpful to improve immunity and is normally advised during the degenerative phase of life, which starts from around 45 years in both men and women. Some of the medicinal plants valued in Ayurvedic Rasayana like *Asparagus racemosus, Achillea wilhelmsii, Acacia catechu, Adhatoda vasica, Aloe vera, Amophophallus companulatus, Azadirachta indica, Bauhinia variegate, Bergenia stracheyi, Capparis zeylanica, Carica papaya, Chlorophytum arundinaeceum, Centella asiatica, Curcuma longa, Dioscorea alata, Enicostemma axillare, Justica spicigera, Mangifera indica, Madhuca longifolia, Ocimum sanctum, Ricinus communis, Tinospora cordifolia, Toxicodendron pubescens, Zingiber officinale* etc., are evaluated for their therapeutic potential and have been scientifically investigated with promising results. A number of plant-based principles have been isolated with potential immunomodulatory activity that can explain and justify their use in traditional medicine in the past and can form the basis for further research in the future as well. This work shall hopefully encourage researchers to undertake further work on medicinal plants with potential immunomodulatory activity.

Keywords: Immunomodulatory, Rasayana, Humoral immunity, Cellular immunity, Ayurvedic plants, Haemagglutination, Phagocytosis

INTRODUCTION

Immunomodulation is a very broad term which denotes any changes in the immune response and may involve induction, expression, amplification or inhibition of any part or phase of the immune response. Modulation may be very specific, which is limited to a given antigen/agent or to a non-specific agent with a general effect on immune response. Stimulation of the immune response is desired for certain people such as immune compromised patient, whereas suppression of the immune response is thought for others, such as transplant recipient, allergic and inflammatory disease patients [1].

Immuno stimulation and immunosuppression both need to be tackled in order to regulate the normal immunological functioning. Hence both immune stimulating 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 [2].

Every country in the world has lists of herbal remedies for the treatment of diseases and different other unwanted conditions in humans [3]. Ayurveda is one of the traditional systems of medicine practiced in India and Sri Lanka and can be traced back to 6000 B.C [4]. Ayurveda, like other medical systems

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practised in the world, originated from folk medicine and now holds a commanding position in the China, Germany etc., Ayurvedic medicines are largely based upon herbal and herbo mineral preparations and have specific diagnostic and therapeutic principles [5]. Modulation of immune responses to alleviate the diseases has been of interest for many years and the concept of 'Rasayana' in Ayurveda is based on related principles [4].

Concept of Rasayana

The word Rasayana, a combination of two words (rasa and ayana), refers to nutrition and its transportation throughout the body. Rasayana therapy enhances the qualities of rasa, enriching it with nutrients so one can attain longevity, improved memory and intelligence, freedom from disorder, youthfulness, excellence of hair, complexion and voice, optimum development of physique and sense organs, mastery over phonetics and brilliance. As a dedicated stream of medication for immune promotion, anti-degenerative and rejuvenating health care, the Rasayana therapy of Ayurveda is known to prevent the effects of ageing and improve the quality of life for healthy as well as diseased individuals. Rasayana is helpful to improve immunity and is normally advised during the degenerative phase of life, which starts from around 45 years in both males and females [6].

Chemotherapeutic agents like Cyclosporine, Tacrolimus, Sirolimus, Azathioprine, Cyclophosphamide etc., which are available today mainly possess immunosuppressive activity and most of them are cytotoxic and exerts a variety of side effects like hepatotoxicity [7] gingival hypertrophy, tremor and increased blood pressure, nephrotoxicity [8]. To minimize unwanted side ffects, botanicals with immunomodulating activity are getting more popular. Although cytokines like interleukins and interferon's, Levamisole are used as immune stimulants, these are not very effective in the long term both because of their cost and adverse effects like agranulocytosis, hypersensitivity etc., Thus, medicinal plants and their active components as a source of immune modulatory agents are gaining importance. Uses of plant products to enhance the phagocytic ability of macrophages and increase the antibody production by B cells have been well documented by several researchers [9-13].

Ayurvedic plants having Immuno modulating activity

A. *Asparagus racemosus* **Willd. (Liliaceae)**

The aqueous root extract of the *Asparagus racemosus* having potential immunoadjuvant that also offers direct therapeutic benefits in less morbidity and mortality. It shows significant Immuno protection against intra-cerebral challenge of live *Bordetella pertussis* cells was evaluated based on degree of sickness, paralysis and subsequent death. Reduced mortality accompanied with overall improved health status was observed in treated animals after intra-cerebral challenge of *B. pertussis* indicating development of protective immune response. Fructo-oligosaccharides from the aqueous extract potentiate natural killer cell activity and it could be an important mechanism underpinning the '*Rasayana*' properties of this plant [14, 15].

B. *Achillea wilhelmsii* **C.Koch (Asteraceae)**

The aqueous extract of *Achillea wilhelmsii* exhibited immuno stimulant activity on both humoral and cellular immune functions in mice at a dose of 100mg/kg. It shows significant increase in the delayed type hypersensitivity at a dose of 100mg/kg also shows stimulatory effect on Haemagglutination titre at all doses [16].

C. *Acacia catechu* **Wild.var. (Leguminosae)**

Aqueous extract of *Acacia catechu* at a dose of 50mg/kg shows significant increase in the neutrophil adhesion to the nylon fibers 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 [17].

A. D. *Adhatoda vasica* **Linn (Acanthaceae)**

B. Oral administration of methanolic, chloroform and diethyl ether extracts of leaves *Adhatoda vasica* at a dose of 400mg/kg in adult male Wister rats significantly increased the percentage neutrophil adhesion to nylon fibers and also found to induce delayed type hypersensitivity reaction

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by sheep erythrocytes were pharmacologically validated for its immunomodulatory properties in experimental animals. Vinothapooshan et al., suggested that the extracts of this plant positively modulates the immunity of the host [18].

E. *Aloe vera* **(L.) Burn. (Liliaceae)**
Intraperitoneal administration of *Aloe vera* extract to Swiss albino mice at a dose of 300mg/kg daily for five days significantly increased the total white blood cells count, humoral immune response and plaque-forming cells in the spleen and circulating antibody titre [19].

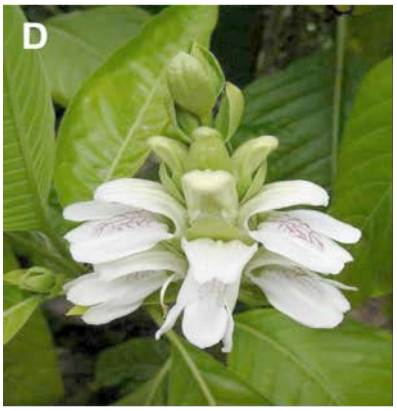
F. *Amorphophallus campanulatus* **Roxb. (Araceae)**
Tripathi et al., suggested that the methanolic extract of *A campanulatus* tuber significantly and dose dependently suppressed the immune system in mice. It exhibits immunomodulatory activity by causing a significant decrease in charcoal clearance, spleen index and delayed-type hypersensitivity response [20].

G. *Azadirachta indica* **A. Juss (Meliaceae)**
Aqueous extract of the stem bark of *Azadirachta indica* showed strong anticomplementary effects which were dose and time-dependent and most pronounced in the classical complement pathway. Intraperitoneal administration of the 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 challenge [21]. Pretreatment of the NIM-76 a volatile fraction from Neem oil resulted in an increase in polymorphonuclear leucocytes with a concomitant decrease in lymphocyte counts. NIM-76 acts through cell-mediated mechanisms by activating macrophages and lymphocytes [22].

H. *Bauhinia variegate* **Linn. (Caesalpiniaceae)**
Ethanolic extract of the stem bark of *Bauhinia variegate* significantly increases the phagocytic index and percentage neutrophil index at doses of 250 and 500 mg/kg/p.o. It holds a promise as an immunomodulating agent, which acts probably by stimulating both the specific and nonspecific arms of immunity [23].

I. *Bergenia stracheyi* **Hook & Thorns (Saxifragaceae)**
Oral administration of Bergenin, a C-glycoside of 4-O-methyl gallic acid, isolated from rhizomes of *Bergenia stracheyi* and its O-demethylated derivative norbergenin0, prepared from bergenin, are reported to show possible modulation of Th1/Th2 cytokine balance. Flow cytometric study showed that these compounds at doses of 5, 10, 20, 40 and 80 mg/kg per oral dose inhibit the production of proinflammatory Th1 cytokines (IL-2, IFN-α and TNF-α) while as potentiate anti-inflammatory Th2 cytokines (IL-4 and IL-5) in the peripheral blood of adjuvant-induced arthritic balb/c mice. This shows the potential Th1/Th2 cytokine balancing activity of **bergenin** and **its derivative** which is strongly correlated with their anti-arthritic activity [24].

J. *Capparis zeylanica Linn***. (Capparidaceae)**
Capparis zeylanica commonly known as Indian caper, is a climbing



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shrub found throughout India and has been used as a rasayan drug in the traditional Ayurvedic system of medicine. Ethanolic and aqueous extracts of leaves on cellular and humoral immune responses to the antigenic challenge by SRBCs and by neutrophil adhesion test, phagocytic activity and cyclophosphamide-induce myelosuppresion. Pretreatment of the aqueous extract of leaves of *Capparis zeylanica* shows significant increase in the neutrophil adhesion to nylon fibers. A dose related increase in both primary and secondary antibody titre was observed. *Capparis zeylanica* extracts prevented myelosuppression in mice treated with cyclophosphamide drug [25].

K. *Carica papaya* **Linn. (Caricaceae)**

Aqueous leaf extract of *Carica papaya* shows significant growth inhibitory activity on tumor cell lines and the production of IL-2 and IL-4 was reduced following the addition of extract, whereas IL-12p40, IL-12p70, IFN-α and TNF-α was enhanced without growth inhibition. Microarray analyses showed that the expression of 23 immuno modulatory genes, classified by gene ontology analysis, was enhanced by the addition of extract. *Carica papaya* leaf extract can mediate a Th1 type shift in human immune system and suggested that the leaf extract may potentially provide the means for the treatment and prevention of selected human diseases such as cancer, various allergic disorders and may also serve as immune adjuvant for vaccine therapy [26].

L. *Chlorophytum arundinaeceum* **Baker (Liliaceae)**

Oral administration of hydro alcoholic extract of roots of *Chlorophytum arundinaeceum* showed a significant increase in the humoral antibody responses, by increasing the hemagglutinating antibody titre at doses of 100 and 200 mg/kg/p.o in Swiss albino mice. There was a significant dose dependent increase in the phagocytic index and percentage neutrophil adhesion. It acts probably by stimulating both the specific and nonspecific arms of immunity [27].

M. *Centella asiatica* **Linn (Apiaceae)**

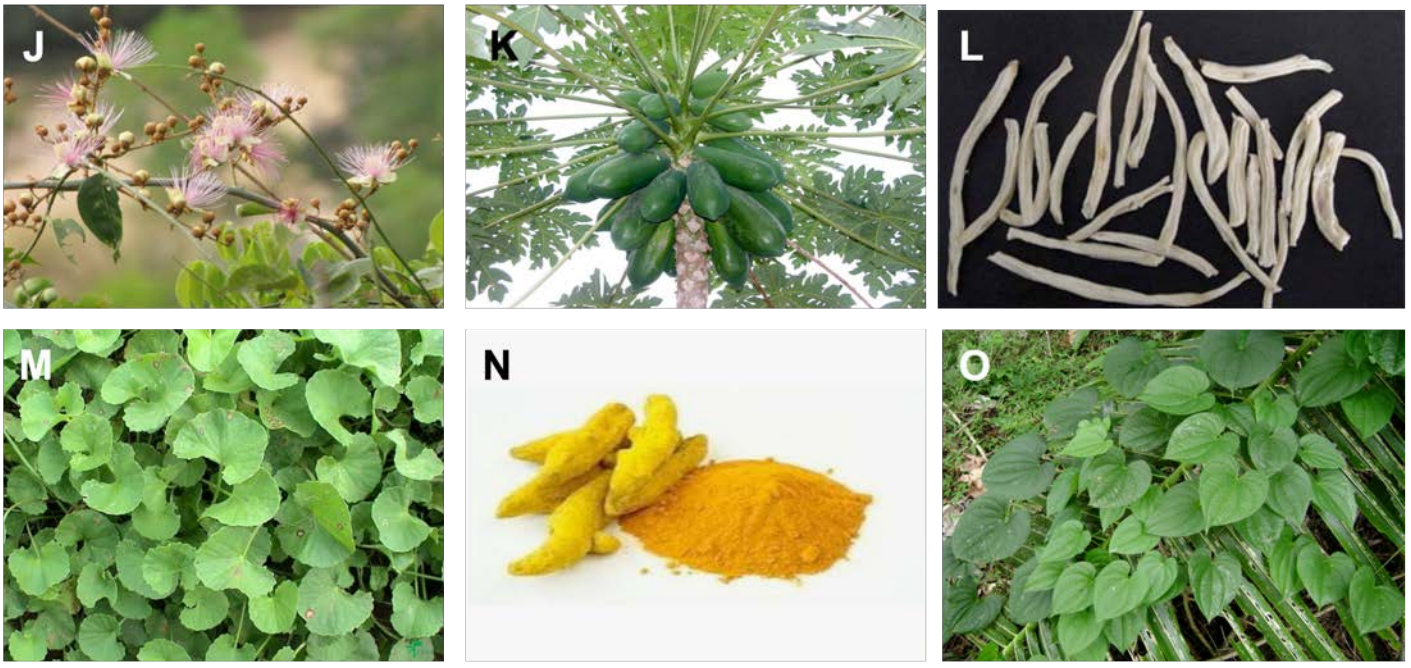
Methanolic extracts of *Centella asiatica* (0.18% w/v of Asiaticoside) and *Eclipta alba* (1.6% w/v Wedelolactone) at five doses of 100, 200, 300, 400 and 500 mg/kg b.w had significantly increased the phagocytic index and total WBC Count evaluated by using carbon clearance test and cyclophosphamide immunosuppression method [28].

N. *Curcuma longa* **Linn (Zingiberaceae)**

Administration of 50 mg/kg *Curcuma longa* rhizome in Swiss albino mice protects from the damaging actions CCl_4 on the non-specific host response in the peritoneal macrophages of these CCl_4 intoxicated mice. It has immunotherapeutic properties along with its ability to ameliorate hepatotoxicity [29]. High polarity fraction of the hot water extract exhibited stimulatory effects on human peripheral blood monocytes proliferation. The cytokine productions (TGF-α, TNF-β, GM-CSF, IL-1α, IL-5, IL-6, IL-8, IL-10, IL-13, etc.) have been modulated by a polysaccharide-enriched fraction. It acts as an adjuvant supplement for cancer patients, whose immune activities were suppressed during chemotherapies [30].

O. *Dioscorea alata* **L. cv. Tainong (Dioscoreaceae)**

Dioscorin isolated from the tuber of *Dioscorea alata* was evaluated for its immune modulatory activity *in vitro* in the presence of polymyxin B to eliminate lipopolysaccharide contamination. 5-100µl of Dioscorin was able to stimulate nitric oxide production



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N: http://www.mgtshop.creamjula.com/index.php/acne-clear-serum.html; O: http://www.onlyfoods.net/dioscorea-alata.html

in RAW264.7 cells. Dioscorin was found to induce IL-6, TNF-α, and IL-1β production in RAW264.7 cells and human monocytes. The stimulated proliferation index of splenic cells ranged from 1.38 to 1.48 fold of phytohaemogglutin (PHA) alone for PHA mixed with different concentrations of dioscorin (10, 25, and 50 mg/ml). Yen-Wenn Liu et al., suggested that, the tuber storage protein of yam dioscorin functions as an immunomodulatory substance [31].

P. *Enicostemma axillare* **(Lam) A.Raynal. (Gentianaceae)**

The methanol extract of *Enicostema axillare* act on both humoral and cell mediated immune functions and decreases the release of pro-inflammatory cytokines in the peritoneal macrophages. Treated with extract appeared to give phagocytic modulation without dose response relationship. Higher concentrations of the extract showed a smaller inhibitory effect and it inhibits the production of $NO^{\cdot}$ significantly in a dose dependent manner. Presence of the compound swertiamarin in crude extract is responsible for the activity [32].

Q. *Justicia spicigera* **Schltdl (Acanthaceae)**

Ethanolic extract of leaves of *Justica spicigera* administrated at doses of 10, 50 and 100 mg/kg i.p. inhibited the tumor growth by 28%, 41% and 53% respectively, in mice bearing human cervical carcinoma cell (HeLa) tumor. *J. spicigera* extract stimulated the phagocytosis of *Saccharomyces cerevisisae* yeasts and the free radicals released by human differentiated macrophages and also stimulated the proliferation of murine splenocytes and induced natural killer cell activity. [33].

R. *Mangifera indica* **Linn (Anacardiaceae)**

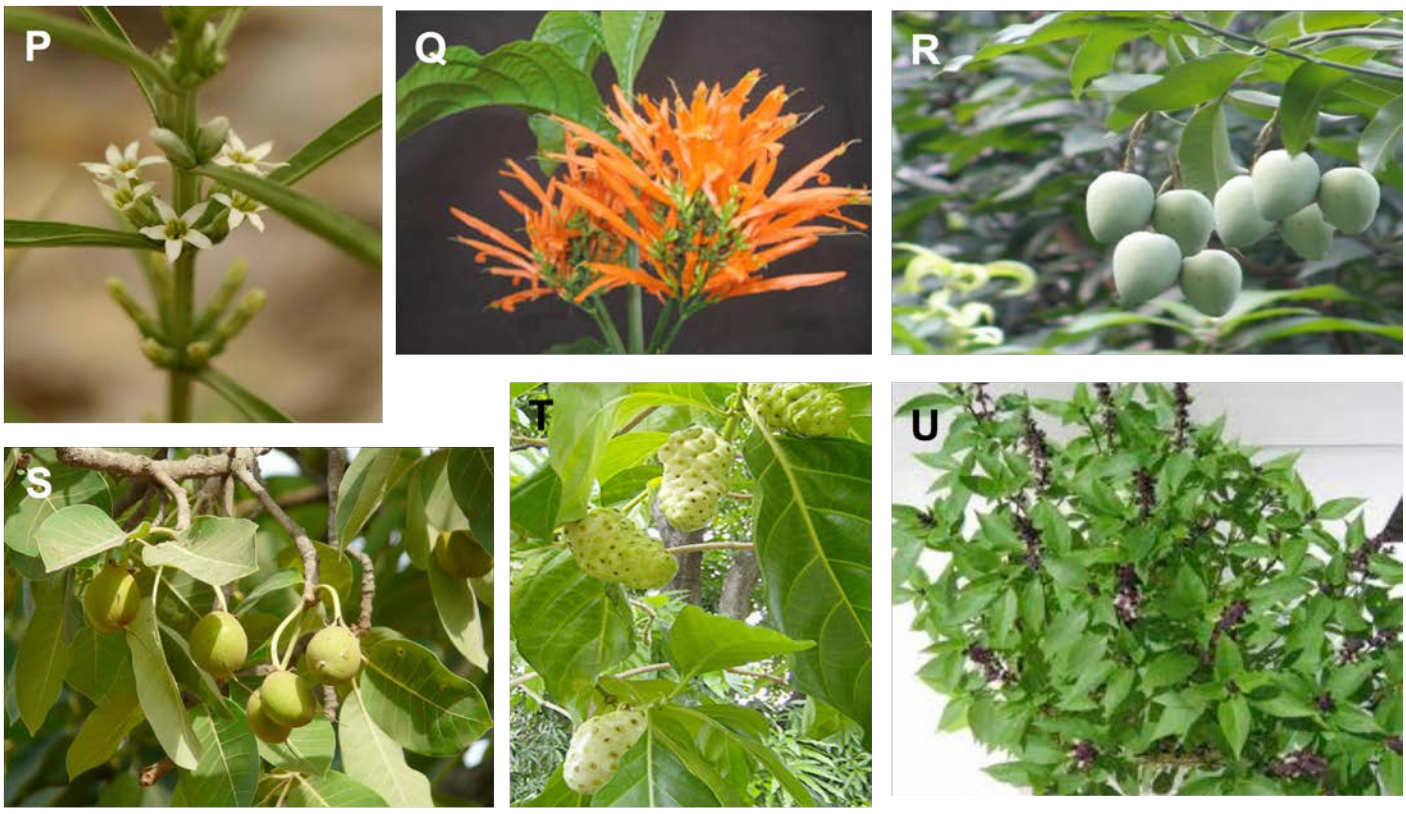
The alcoholic extract of stem bark of *Mangifera indica* containing mangiferin 2.6% has been investigated for its effect on cell mediated and humoral components of the immune system in mice. Administration of extract to the Swiss albino mice at a dose of 50 to 800mg/kg per oral, higher doses 200,400 and 800mg/kg produces significant increase in humoral antibody titre and delayed type hypersensitivity in mice and the extract is having a promising drug with immunostimulant properties [34].

S. *Madhuca longifolia Var.latifoli* **(Sapotaceae)**

Ethanolic extract of the whole plant of *Madhuca latifolia* shows an enhanced humoral immune response on 7th day by 13% as compared to the cyclophosphamide that exhibited 54% humoral immune response, whereas cell mediated immune response was observed with an enhancement in the values (20.27%) when compared with cyclophosphamide (37.63%) [35].

T. *Morinda citrifolia* **Linn** *(Rubiaceae)*

The stimulatory effects of the extracts of *M.citrifolia* fruits on important components of the adaptive immune system such as T lymphocytes and B lymphocytes were studied. The effects of the plant extracts on lymphocytes were assessed by *in vitro* MTT



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assay and *in vivo* (Cell mediated immune response) techniques. The MTT study indicated that the hydroalcoholic (0.5 and 1.0mg/mL) and aqueous extracts (0.5 and 1.0mg/mL) significantly ($p < 0.05$) increased *in vitro* splenocyte proliferation to the extent of 43.6, 54.5, 32.7, and 36.4%, respectively. Moreover,the hydroalcoholic (200 mg/kg) and the aqueous (200 mg/kg) extracts significantly ($p < 0.05$) increased the cell-mediated immune response to the extent of 33.52 and 18.56%, respectively [36].

U. *Ocimum sanctum* **Linn. (Meliaceae)**

Aqueous leaf extract of *Ocimum sanctum* have stimulatory effect on T and B lymphocytes particularly on T-helper subset of lymphocytes by enhancement in IL-2 production. The extract shows the significant enhanced ability of spleen cells to secrete IL-2. It improves overall body constitution by increasing haemoglobulin, leukocytosis and lymphocytosis [37]. Several researchers have confirmed repeatedly that *O.sanctum* increases both specific and nonspecific immunity [38, 39, 40]. *Ocimum sanctum* seed oil significantly increased the anti-sheep red blood cells antibody titre value and decreases the percentage of histamine release from peritoneal mast cells of sensitized rats (humoral immune responses) and also decreased the footpad thickness and percentage of leucocyte migration inhibition. It appears to modulate both humoral and cell-mediated immune responsiveness and these immune modulatory effects may be mediated by GABAergic pathways [41]. 300mg capsules of ethanolic extracts of leaves of *O.sanctum* was through a double blind randomized controlled cross-over trial on healthy volunteers shows statistically significant increase in the levels of IFN-γ, IL-4 and percentages of T-helper cells and Natural killer cells were observed after 4 weeks in the extract intervention group in contrast to the placebo group [42].

V. *Ricinus communis* **Linn (Euphorbiaceae)**

The isolated tannin compounds from the methanolic leaf extract of *Ricinus communis* significantly increased the phagocytic function of human neutrophils and neutrophil chemotactic movement as indicated by the increase in number of cells reaching the lower surface of filter; therefore, the study result revealed that, the extract acts as a chemo attractant which exhibited by increase in the intracellular reduction of Nitroblue tetrazolium dye to formazan by the neutrophils and confirms the intracellular killing property and overall metabolic integrity of phagocytosing neutrophils. Tannins obtained from the extract possess anti-inflammatory and immune modulatory properties [43].

W. *Tinospora cordifolia* **(Willd) Miers ex Hook. F & Thomas (Menispermaceae)**

Ethylacetate, water fraction and hot water extract of stem of *Tinospora cordifolia* significantly increased the phagocytic function of human neutrophils. Seven compounds of different classes such as alkaloids, phenylpropanoids and sesquiterpenes were isolated from the active fractions out of which two cordifolioside A and syringin were reported to have immune modulatory activity [44, 45, 46]. Remaining compounds showed significant enhancement in phagocytic activity and increase in nitric oxide reactive oxygen species generation at a concentration between 0.1 to 2.5 µg/ml [47]. The immuno modulatory activity of *T. cordifolia* may be attributed to the synergistic effect of groups of compounds present in the particular fraction.

X. *Toxicodendron pubescens* **Mill (Anacardiaceae)**

10 mg/kg of the powdered crude sample of *T.pubescens* in 0.5% carboxy methyl cellulose shows the stimulation of phagocytosis, Candidacidal activity and chemotaxis of human PMN cells [48].

Y. *Zingiber officinale* **Roscoe (Zingiberaceae)**

The volatile oil of ginger (0.001to10ng/mL) significantly inhibited T lymphocyte proliferation, decreased the number of the total T lymphocytes and T helper cells in a concentration-dependent manner, but increased the percentage of T suppressor cells to the total T lymphocytes in the mice. In addition, the volatile oil of ginger inhibited IL-1α secretion by the mice peritoneal macrophages in a concentration-dependent manner. Oral administration of the volatile oil of ginger in the doses of 0.125, 0.25 and 0.5g/kg body weight dose-

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dependently weakened the delayed type of hypersensitivity response to 2, 4-Dinitro-1-fluorobenzene in the sensitized mice. Hua-li Zhou et al [49] suggested that it influences both cell-mediated immune response and nonspecific proliferation of T-lymphocyte, and may exert beneficial effects in a number of clinical conditions, such as chronic inflammation and autoimmune diseases.

Conclusion

From the above review it should be evident that, there are many medicinal plants which exert immune modulatory 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., *Ocimum sanctum*, *Tinospora cordifolia*) and some may suppress the immune response. Also, various secondary metabolites (e.g., alkaloids, glycosides, saponins, flavonoids, coumarins and sterols) exhibit a wide range of immune modulating activity. This review describes the variety of approaches that have been undertaken to establish the immune modulating activity of Indian herbal plants.

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