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A Review on Immunomodulatory Medicinal Plants

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Abstract

The ayurvedic system of medicine is one of the oldest systems of medicine and includes various ethnopharmacological activities such as immunostimulation, tonic, neurostimulation, anti-ageing, antibacterial, antiviral, antirheumatic, anticancer, adaptogenic, etc. An entire section of the Materia Medica of Ayurveda is devoted to "Rasayana", drugs reputed to enhance body resistance. Listed as a class in the texts of traditional Indian Medicine literature, Rasayana consists of a number of plants reputed to promote physical and mental health, improve defense mechanisms of the body and enhance longevity. These attributes are similar to the modern concept of adaptogenic agents, which are known to afford protection of the human physiological system against diverse stressors. A number of medicinal plants as Rasayanas have been claimed to possess immunomodulatory activity. The present review highlights the use of various medicinal plants as immunomodulators.

Key-words: Ayurveda, Medicinal plants, Immunomodulators.

Introduction

Medicinal plants have tremendous potential to yield novel compounds as model for future drugs. One of the fast developing area of drug development involves the search for novel immunomodulatory agents having either immune-stimulatory or immune-suppressant activity that could be used for the treatment of various immune dysfunctions or in case of residual cancer. The intralesional application of BCG and systemic use of chemical non-specific immunomodulator levamisole have shown promising results, however, break-through in the field of immunomodulators was achieved when a strong immunosuppressant drug, cyclosporine was discovered that prevented the rejection of graft and had use in other auto-immune diseases. Immu-21 a polyherbal immunomodulator has been reported to promote host immune functions by augmenting both arms of the immune system i.e. humoral and cell-mediated immunity and has been reported to be safe and non-toxic. There are a number of medicinal plants whose crude preparations, formulations or purified compounds have shown strong immunomodulatory activity. [1-4]

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Medicinal Plants as Immunomodulators [7-31]

Curcuma longa

Curcumin, an active ingredient of *Curcuma longa* ('Haldi' or Turmeric, Family: Zingiberaceae) and powdered root extract from *W. somnifera* (20 mg/dose/animal, i.p) were found to increase total WBC count, increase in circulating antibody titre against Sheep Red Blood Corpuscles (SRBC), splenic plaque forming cells (PFC), bone marrow cellularity, alpha esterase positive cells and an increase in the phagocytic activity of macrophages in BALB/c mice. The petroleum ether extract of the rhizomes of *C. longa* also showed significant anti-inflammatory activity and was effective in delayed hypersensitivity.

***Piper betle* Linn**.

It is a widely distributed plant in the tropical and subtropical regions of the world and has been attributed as traditional herbal remedy for many diseases. *P. betle* has several landraces. The *in vivo* immunomodulatory efficacy in the crude methanolic extract and its n-hexane, chloroform, n-butanol fractions of the female plant at various doses in murine model. The crude methanol extract and n-hexane fraction were found to potentiate both the humoral (PFC and hemagglutination titre) and cellular (lymphoproliferation, macrophage activation, delayed type hypersensitivity) immune responses in mice. The splenocytes of treated mice displayed enhanced population of CD4+ and CD8+ T cells as well as CD19+ B cells. The n-hexane fraction induced a biased type 2 cytokine response (increased IL-4, decreased IFNγ) while the chloroform fraction produced a predominant type 1 cytokine response. On the other hand, the crude methanolic extract possessed a mixed T_H cell response suggesting a remarkable immunomodulatory property in this plant.

***Nepeta ucrainica* L.**

Phytochemical investigations of the aerial parts of the plant *Nepeta ucrainica* L. (used as herbal tea in Kazakhistan) resulted in the isolation of verbascoside. The *in vitro* immunomodulatory activity of verbascoside was investigated by assessing neutrophil function, chemotaxis and intracellular killing activity. Verbascoside showed an increased chemotactic activity and had a positive effect on respiratory burst of neutrophils. The opposite effect was observed with increasing doses demonstrating a possible suppression of neutrophil intracellular killing activity.

Tinospora cordifolia

Also known as Guduchi belongs to family Menispermaceae has been reported to contain a polysaccharide as an immunomodulatory constituent in its crude stem extract and was found to impart its effect as an adjuvant to augment process of ulcer healing, bacterial eradication and polymorphonuclear phagocytosis.

Alpinia galanga

Another polysaccharide isolated from the rhizome of *Alpinia galanga* showed a marked stimulant effect on the reticulo-endothelial system (RES) and increased the cellularity in the peritoneal cavity as well as in spleen after treatment of mice. "Ginseng", a well known herbal remedy, developed mainly from the roots of Korean or

Panax ginseng

Asian ginseng (*Panax ginseng*), Siberian ginseng (*Eleutherococcus senticosu*), or American ginseng (*Panax quinquefolius*), belong to family Araliaceae was reported to impart its immunomodulatory functions by increasing antibody concentration and natural killer (NK) cell activity in the treated individuals. It has also been reported to confer a lower incidence of influenza and colds. The main active agent in *Panax ginseng* is identified as ginsenoside, a triterpene saponin.

***Mollugo verticillata* L.**

An independent study with ethanolic extracts of *Mollugo verticillata* L. (Family: Molluginaceae) has confirmed stimulation of peritoneal macrophages and increased production of nitric oxide (NO), however, if used along with BCG or *Mycobacterium tuberculosis* antigen, it suppressed the activity of these cells. An aqueous extract prepared from the fruits of the plant

Emblica officinalis

Also *Phyllanthus emblica*; Family: Euphorbiacae has been shown to possess antioxidant properties and protected mice from the chromosome-damaging effects of the well known carcinogen 3, 4-benzo (a) pyrene thereby increasing the life span of tumor bearing mice. Immunomodulatory effects of the aqueous extract of the tea, *Camellia sinensis*, was also reported *in vitro* in the form of enhanced production of neopterin, a sensitive

marker of cell-mediated immunity (CMI) in un-stimulated human peripheral mononuclear cells, however, a reduction of neopterin formation was observed when cells were stimulated with mitogens.

Centella asiatica

Another important traditional medicinal plant, *Centella asiatica* (Family: Apiaceae) commonly known as "Mandukaparani" in India, is used in folk medicine as rasayana. The alcoholic extract of *C. asiatica* has been reported to have reticulo-endothelial stimulating activity and increases the antibody titer and delayed type hypersensitivity (DTH) response when fed at 100 mg/ kg body weight. The active constituent of *C. asiatica* was identified as Asiaticosides.

Azadirachta indica

The Indian Vedic plant Neem *(Azadirachta indica,* Family: Meliaceae) is also a powerful immunostimulatory plant reported to be non-toxic and hematostimulatory.

Andographis paniculata

The methanolic extract of *Andographis paniculata* (Family: Acanthaceae), also known 'Kaal Megh, has been reported to contain andrographolide, 14-deoxyandrographolide and 14-deoxy-11, 12-didehydroandrographolide as active constituents which are attributed with the strong immunostimulatory properties. These compounds enhanced the cellular proliferation and interleukin-2 (IL-2) production in human peripheral blood lymphocytes and reversed the cyclophosphamide induced immunosuppression.

Chlorophytum borivilianum

A polysaccharide fraction derived from hot water extraction of *Chlorophytum borivilianum* (Family: Liliaceae) comprising ~31% inulin-type fructans and ~25% acetylated mannans was found to stimulate NK cell activity *in vitro*, however, *in vivo* evaluation of the aqueous extract was found to strengthen the humoral immune functions of Wistar strain of albino rats.

Prominent work of herbal Medicine [32-50]

A study conducted by Dhuley with plants *Asparagus racemosus, Tinospora cordifolia, Withania somnifera* and *Picrorhiza kurroa* revealed significant attenuation of ochratoxin carcinogen induced suppression of chemotactic activity as well as IL-1 and TNFα production by macrophages of treated mice. These plants also produced leucocytosis with predominant neutrophilia and prevented, to varying degrees, the leucopenia induced by cyclophosphamide. The plant *A. racemosus* induced excessive production of TNFα while *W. somnifera* potentiated macrophage chemotaxis, NO production over that of controls. Immunostimulatory effects have also been reported from the bark aqueous extract of *pule* (*Alstonia scholaris*, Family: Apocynaceae) in BALB/c mice. The extract stimulated non specific immune response, restored the prednisolone induced reduction of phagocytic activity and protected the body from opportunistic infection caused by *Escherichia coli*. The hexane and aqueous extracts/ fractions of *Carica papaya* seeds significantly enhanced the proliferation of lymphocytes towards phytohemagglutinin (PHA) sensitization and inhibited the classical complement-mediated hemolytic pathway.

Among the numerous plants known for their traditional medicinal use, *Pterospermum acerifolium* commonly known as Kanak Champa was also reported to have hepatoprotective activity. Preliminary phytochemical analysis of the leaf extract of this plant revealed the presence of several compounds like steroids, flavonoids, alkaloids and glycosides. We have reported a contrasting immunomodulatory activity in different vegetative parts of this plant i.e. a strong immunosuppressive activity in the seed part and an excellent immunostimulatory activity in the floral ethanolic extract derived from this plant demonstrating the diverse pharmacological activity in different parts of the same plant. *Withania coagulans* has been ascribed to possess various biological activities including anti-hyperglycemic activity. This plant is known to contain withanolides (withaferin-A), phenolic tannin, flavonoids and flavonols. Shah and Juvekar have reported the macrophage activating effects in the form of up-regulated production of nitric oxide and augmentation in the antibody levels of animals treated with an aqueous extract from the leaves of *Murraya koenigii*, commonly known as curry leaf tree (Family: Rutaceae). *M. koenigii* extract has also been reported to have anti-hyperglycemic and cholesterol lowering effects. Bafna and Mishra described the *in vitro* antioxidant and immunomodulatory activity in mice treated with the alkaloidal fraction from the

roots of *Cissampelos pareira* Linn in a dose dependent manner. The alkaloid fraction was found to have significant immunosuppressive activity at lower doses (25 and 50 mg/kg) while no activity was observed at higher doses (75 and 100 mg/kg) revealing the immunosuppressive and antioxidant activities in the alkaloidal fraction of *C. pareira* roots. Khanfor the first time have reported immunomodulatory activity in the ethanol (50%) extracts of the seed and root of *Nyctanthes arbortristis* L. against systemic candidiasis in mice. Sharififar demonstrated immunomodulatory activity of the aqueous extract from the fruits of *Heracleum persicum* Desf. (Apiaceae) at 50, 100 and 200 mg/kg in female Swiss mice. The extract was found to stimulate both humoral and cellular arms of the immune system. The alkaloids, tetrandrine found in the roots of *Cyclea arnotii* Miers (Family: Menispermaceae) and rohitukine present in the stem bark of *Dysoxylum binectariferum* Hook. f. (Family: Meliaceae) also possessed immunomodulatory properties and plant has been indicated in the treatment of various immune disorders.

The hexane, chloroform and ethanol extracts of *Boerhavia diffusa* (Commonly known as Punarnava, Family: Nyctaginaceae) were evaluated *in vitro* for their immunomodulatory activities on human peripheral blood mononuclear cells (PBMCs). The hexane extract was found to stimulate proliferation of PBMCs, LPS induced NO production and, PHA/ LPS induced IL-2 and TNFα production. The pure compound Bd-I (eupalitin-3-O-h-D galactopyranoside) purified from the ethanolic extract inhibited production of PHA stimulated IL-2 at the protein and mRNA transcript level and LPS stimulated TNFα production in human PBMCs at equivalent dose. This compound also blocked the activation of DNA binding of nuclear factor-ќ B and AP-1, the two major transcription factors centrally involved in expression of IL-2 and IL-2R gene, which are necessary for the activation and proliferation of T cells.

Conclusion

Plants have served a great deal in treating various diseases and maintaining good health. There is huge information available on several plants and each plant is having several traditional and scientifically established therapeutic uses. Several researchers have reviewed literature on several categories of drugs and medicinal plants. This list of this literature survey is restricted to the conventional and historical uses and its therapeutic effect on the physiology has been reported in reputed journals on the plants used in this study. Several review articles, research papers, text books, and databases are referred over a wide period. The literature available on the marketed imunomodulators used in this study.i.e. various Ayurvedic Marketed to increase immunity.

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