REVIEW ARTICLE

Indian medicinal plants used as immunomodulatory agents: A review

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Abstract

India is a country with rich biodiversity and enormous treasure of medicinal plants and consequently called as medicinal garden of the world, many indigenous systems such as Ayurveda, Yoga, Unani, Homeopathy, Naturopathy, and Siddha are well-known and practiced in India from decades. A large number of Indian medicinal plants have been reported to possess immunostimulant activity and thus can serve as potential source of drug in various immunocompromised states such as AIDS, cancer, and for treatment of various chronic infections. At present, there is much-growing interest in the use of these medicinal plants as modulators of the complex immune system. Many therapeutic effects of plant extracts have been suggested to be due to their wide array of immunomodulatory effects and influence on the immune system of the human body. Phytochemicals such as flavonoids, lactones, alkaloids, and glycosides, present in several plants, have been reported to be responsible for the plant's immunomodulating properties. Thus, the search for natural products of plant origin as new leads for the development of potent and safe immunosuppressant and immunostimulant agents is gaining much major research interest. Keeping in mind, the tremendous potential of the medicinal plants and their derived drugs, this review also discusses biological screening methods for various plant drugs that focus on revealing the mechanism involved in immunomodulation. This review further focuses on the various medicinal plants available in India used to enhancement and suppresses of impaired immune system under unfavorable conditions.

Key words: Immune system, immunomodulatory, immunosuppressive, Indian medicinal plants

INTRODUCTION

Modulation of immune functions using medicinal plants and their products as a possible therapeutic measure has become an accepted therapeutic approach. Plants and minerals have been used since ancient times for the treatment of many ailments and diseases. It is now being recognized that immunomodulation of immune response could provide an alternative to conventional chemotherapy for a variety of disease conditions, especially when the host's defense mechanism has to be activated under conditions of impaired immune responsiveness or when a selective immunosuppressant has to be induced in situation such as autoimmune disorders and organ transplantation. Immunity is a homeostatic process, a series of delicately balanced complex, multicellular and physiologic mechanisms that allow an individual to distinguish foreign material from "self" and neutralize and/or eliminate the foreign matter.[1]

CLASSIFICATION OF IMMUNOMODULATORS

The immune system is a complex system, involving an interwoven network of biochemical mechanisms. The modulation of immune response by various agents to alleviate the disease has been of interest since many years, to modulate and potentiate the weapons of your immune system keeping them in a highly prepared state for any threat it may encounter. With this balancing effect, all subsequent immune responses improve. When your immune system

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is in this highly prepared state, the invading organisms do not have the time to build up force and strength before the immune system attack destroys and/or weakens the invader. Immunomodulation is the process of modifying an immune response in a positive or negative manner by administration of a drug or compound. Many proteins, amino acids, and natural compounds have shown a significant ability to regulate immune responses including interferon-γ (IFN-γ) and steroids. These substances, which can stimulate, suppress, or modulate any of the immune system, including both adaptive and innate arms of the immune response. Clinically, immunomodulators can be classified into the following three categories.[2]

IMMUNOADJUVANTS

These agents are used to enhance the efficacy of vaccines and, therefore, could be considered specific immunostimulants. Immunoadjuvants hold the promise of being the true modulators of the immune response.[3]

IMMUNOSTIMULANTS

These are inherently non-specific as they are envisaged as enhancements to a body's resistance to infection. They can act through innate as well as adaptive immune responses. In healthy individuals, the immunostimulants are expected to serve as prophylactic and promoter agents, i.e., as immunopotentiators, by enhancing the basic level of immune response. In the individual with impairment of immune response, they are expected to act as immunotherapeutic agents.[4]

IMMUNOSUPPRESSANTS

These are a structurally and functionally heterogeneous group of drugs, which are often concomitantly administered in combination regimens to treat various types of organ transplant rejection and autoimmune diseases.[5]

METHODS FOR TESTING IMMUNOLOGICAL FACTORS

The routine process for screening is to extract single ingredient or single distilled fraction from herbal drugs, determine its bioactivity by the classic pharmacological means. The whole animal model is the most classic pharmacological screening model, which is very important at the aspect of medicine evaluation because it can apparently respond to the efficacy, side effect, and toxicity of medicines in whole. Although this method is high cost and low efficient, at present, it is still a primary way to drug discovery and evaluation. Several *in vitro* and *in vivo* methods of pharmacological screening of medicinal plants having immunomodulatory activity have been reported.[6]

In Vitro Methods

1. Inhibition of histamine release from mast cells
2. Mitogens induced lymphocyte proliferation
3. Inhibition of T-cell proliferation
4. Chemiluminescence in macrophages
5. Plaque-forming colony test
6. Inhibition of dihydroorotate dehydrogenase.

In Vivo Methods

1. Spontaneous autoimmune diseases in animals
2. Acute systemic anaphylaxis in rats
3. Anti-anaphylactic activity (Schultz-Dale reaction)
4. Passive cutaneous anaphylaxis
5. Arthus type immediate hypersensitivity
6. Delayed-type hypersensitivity
7. Reversed passive Arthus reaction
8. Adjuvant arthritis in rats
9. Collagen type II-induced arthritis in rats
10. Proteoglycan-induced progressive polyarthritis in mice
11. Experimental autoimmune thyroiditis
12. Coxsackievirus B3-induced myocarditis
13. Porcine cardiac myosin-induced autoimmune myocarditis in rats
14. Experimental allergic encephalomyelitis
15. Acute graft versus host disease in rats
16. Influence on SLE-like disorder in MRL/lpr mice
17. Prevention of experimentally induced myasthenia gravis in rats
18. Glomerulonephritis induced by anti-basement membrane antibody in rats
19. Autoimmune uveitis in rats
20. Inhibition of allogeneic transplant rejection.[7-10]

The list of Indian plants having immunomodulatory activity is summarized in Table 1.

CONCLUSION

Modulation of the immune responses through the stimulatory or suppressive activity of a phytoextract may help maintain a disease-free state in normal or unhealthy people. Agents that activate host defense mechanisms in the presence of an impaired immune response can provide supportive therapy to conventional chemotherapy. This article will give an overview of the important medicinal plants having immunomodulatory activities, which can provide an alternative to conventional chemotherapy for a variety of diseases, especially when host defense mechanism has to be impaired under the conditions of impaired immune responses when a selective immunosuppression is desired in situation like autoimmune

Table 1: List of Indian medicinal plants having immunomodulatory activity[11-65]

Plant name	Tissue	Chemical constituents	Model used
Acacia catechu Willd.	Leaf	Tannins and flavonoids	Neutrophil adhesion and carbon clearance test
Acanthopanax sessiliflorus (Rupr. and Maxim.)	Shoots and roots	Biopolymers	Lymphocyte-proliferating effects
Artemisia annua Linn.	Herb	Artemisinin	DTH and lymphocytic proliferation assay
Achillea millefolium C. Koch	Leaves	Flavonoids, alkaloids, and coumarins	DTH, hemagglutination
Aloe vera Tourn. ex Linn.	Gel from leaves	Anthraquinone glycosides	Hematological, serological studies
Allium sativum	Bulbs	Allicin	Hemagglutination
Aesculus indica	Leaf	Alkaloids, saponins, and tannins	Neutrophil index, neutrophil adhesion
Andrographis paniculata Nees	Leaves	Diterpenes	DTH mouse model
Asparagus racemosus Wild.	Roots	Saponins and sitosterols	SRBC-sensitized animals
Argyreia speciosa	Roots	Glycosides	Cellular and humoral immunity DTH reaction
Abutilon indicum Linn.	Whole plant	Flavonoids and triterpenoids	HA titer, DTH response, neutrophil adhesion test, and carbon clearance test
Abrus precatorius	Seeds	Alkaloids, phenolics, tannins, and saponins	HA titer, DTH response, PI
Adhatoda vasica Linn.	Leaves	Quinazoline vasicinone and essential oils	Neutrophil adhesion, DTH
Azadirachta indica	Flowers	Azadirachtin	Antibody titer phagocytic activity, nitro blue tetrazolium dye, and DTH reaction
Bauhinia variegata Linn.	Root and bark	Flavonoids, β-sitosterol, and lupeol	Human neutrophils
Boerhaavia diffusa	Herb	Alkaloids	Circulating antibody titer
Balanites roxburghii	Leaf	Alkaloids, flavonoids, tannins, and saponins	Carbon clearance test and serum immunoglobulin
Chlorophytum borivilianum	Roots	Polysaccharides	Phagocytosis using carbon clearance method
Cleome gynandra Linn.	Leaf, seeds, and roots	Hexacosanol and kaempferol	Carbon clearance test, DTH, antibody titer
Calendula officinalis L.	Flowers	Polysaccharides, proteins, and fatty acids	Phagocytosis
Centella asiatica Linn.	Herb	Triterpenoid saponins	Cell-mediated and humoral immune responses
Clitoria ternatea (Linn.)	Aerial parts	β-sitosterol and kaempferol	DTH, antibody, drug-induced myelosuppression
Curcuma longa	Rhizome	Curcumin	Humoral antibody response to SRBC
Citrus aurantifolia	Fruits	Volatile oils	Cell proliferation assay and immunoblotting
Capparis zeylanica	Leaf	Flavonoids	Phagocytosis, delayed hypersensitivity
Cissampelos pareira	Roots	Alkaloids	Humoral antibody titer
Caesalpinia bonducella	Seeds	Flavonoids, alkaloids, tannins, and amino acids	Neutrophil adhesion test and HA
Cleome gynandra	Aerial parts	Flavonoids, alkaloids, terpenoids, and steroids	Carbon clearance method, cell-mediated immunity, immunostimulatory

(Contd...)

Table 1: *(Continued)*

Plant name	Tissue	Chemical constituents	Model used
Eclipta alba L.	Leaves	Triterpenoid glycosides	Phagocytic index and antibody titer
Euphorbia hirta Linn.	Herb	Quercitol, myricitrin, and gallic acid	Phagocytic index
Ficus carica	Leaf	Phenolic compound, phytosterol, and volatile oils	Cellular immune response and humoral antibody response
Ficus benghalensis	Root	Alkaloids, steroids, flavonoids, and tannins	Hypersensitivity and hemagglutination reactions.
Ganoderma lucidum (Fr.) P. Karst	Whole plant	Flavonoids, triterpenes, and polysaccharides	Proliferation of lymphocytes
Gymnema sylvestre	Leaves	Alkaloids, tannins, and flavonoids	Neutrophil locomotion and chemotaxis test
Habenaria intermedia	Tubers	Alkaloids and phenolic compounds	DTH test, carbon clearance test for phagocytic activity
Hyptis suaveolens (L.) Poit. (Lamiaceae)	Leaf and flowers	Lupeol and β-sitosterol	Humoral immune response and lipid peroxide enzyme
Hibiscus rosa-sinensis	Flowers	Alkaloids, flavonoids, terpenoids, and tannins	Carbon clearance method, cell-mediated immunity, immunostimulatory
Lycium barbarum Linn.	Fruits	Polysaccharide-protein complexes	HA PI lymphocytic proliferation
Moringa oleifera L.	Leaves	Vitamin A, B, C, carotenoids, and saponins	DTH test neutrophil adhesion, HA
Morus alba Linn.	Fruits, leaves, and bark	Flavonoids, anthocyanins	Humoral immunity, serum immunoglobulin
Murraya koenigii (L.) Spreng.	Leaves	Coumarins, carbazole alkaloids, glucoside	PI, nitric acid assay, humoral antibody, DTH reaction
Mangifera indica	Stem bark	Alkaloids, tannins, and flavonoids	Humoral antibody response to SRBC
Nyctanthes arbortristis	Leaf	Iridoid glucosides	Humoral immunity, DTH
Ocimum sanctum Linn.	Entire plant	Essential oils such as eugenol, carvacrol, derivatives of ursolic acid, apigenin	Enhance the production of RBC, WBC, and hemoglobin
Picrorhiza kurroa	Leaf	Alkaloids, flavonoids, tannins, and saponins	Cell-mediated and humoral components
Piper longum L.	Fruits	Alkaloids	HA, PI, macrophage migration index
Panax ginseng Wall.	Fruits and root	Ginsenosides, panaxdiol, panaxtriole, and oleanolic acid	Antibody plaque-forming cell response and circulating antibody titer against sheep erythrocytes
Salacia chinensis	Roots	Flavonoids, tannins, alkaloids, and carbohydrates	HA titer, DTH response
Silybum marianum L.	Flowers	Flavonoids	Macrophage migration index
Salicornia herbacea	Herb	Polysaccharides	Phagocytic activity on opsonized
Syzygium cumini	Seeds	Alkaloids, flavonoids, glycosides, and phytosterols	Carbon clearance method and hemagglutination titer, DTH
Terminalia arjuna Roxb.	Leaves and bark	Flavonoids, oligomeric proanthocyanidins, and tannins	Hemagglutination
Tinospora cordifolia Miers.	Entire herb	Alkaloids	DTH and bone marrow cellularity
Trapa bispinosa	Fruits	Flavonoids, proteins, and carbohydrates	Neutrophils, hemagglutination titer

(Contd...)

Table 1: *(Continued)*

Plant name	Tissue	Chemical constituents	Model used
Tridax procumbens	Aerial parts	Tannins, flavonoids, alkaloids, and steroids	DTH model
Urena lobata Linn.	Fruits	Flavonoids and glycosides	Phagocytic activity
Withania somnifera	Root	Withanolides	Bone marrow cellularity

DTH: Delayed-type hypersensitivity, RBC: Red blood cell, WBC: White blood cell, SRBC: Sheep red blood cell, HA: Hemagglutination antibody, PI: Phagocytic index

disorders. Only a few plants have been screened for immunomodulatory activities. From the above review, it is evident that there are several medicinal plants which have immunomodulatory activity, but inadequate evidence does not allow their uses in clinical practice. Therefore, there is a need to explore these plants having medicinal significance. From the present 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 and some may suppress the immune response. Furthermore, various secondary metabolites, such as alkaloids, glycosides, saponins, flavonoids, coumarins, and sterols, exhibit a wide range of immunomodulating activity. Only a few plants have been screened for immunomodulatory activities. From this review, it is evident that there are several medicinal plants which have immunomodulatory activity but many more evidences are required to explore them for clinical practice. Therefore, immunomodulatory agents will gain more importance in the future research of herbal medicine due to their high efficacy, low cost, and low toxicity.

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