

REVIEW ARTICLE

Immunomodulators: Role of medicinal plants in immune system

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ABSTRACT

A broad range of health-care practices is required to exploit the beneficial effects of Ayurveda, which is the most ancient system of medicines. Being the essence of Ayurvedic medicines, Indian medicinal plants manifest miraculous effects in curing a vast range of diseases and disorders among humans and can be better called as “elixirs of life.” Currently, there is much growing interest in the use of these medicinal plants as modulators of the complex immune system. Through a number of vast researches conducted in the area, it is being explored that many of the chemicals in the form of alkaloids, flavonoids, terpenoids, polysaccharides, lactones, and glycoside products are responsible to cause alterations in the immunomodulatory properties. Keeping in mind, the tremendous potential of the medicinal plants and their derived drugs, I am introducing this review with a purpose to globally popularize the Indian herbal medicines as immunomodulators.

KEY WORDS: Immunomodulators; Medicinal Plants; Immunostimulators; Immunosuppressor


INTRODUCTION

It is an evident from the human history that medicinal plants have been the treatment regimen to cure a variety of diseases, including diseases caused by insects, fungi, bacteria, and viruses. The effects shown by the plants are due to the chemicals present in them and they work in the same manner as the conventional drugs. However, there are equally chances for these plants to have some potential harmful and toxic effects also. These undesired side effects can be reduced by processing of the plant's crude product. Ethnobotany is the study of traditional plants for their medicinal properties and is an effective method to discover future medicines. According to 2015-16 data, more

than 300 plants have been identified to have therapeutic potential.^[1]

Around 122 chemicals derived from plants have been identified as therapeutic substances which are also used in commercial drugs, for example, bark of willow tree is very rich in salicylic acid, which is also an active metabolite of aspirin, and this bark has been used from ancient times as a pain killer and antipyretic substance.^[2] Some of the drugs which are frequently used by the physicians are also derived from plant sources, for example, aspirin, digoxin, quinine and opium, etc.^[2] They have a long history of use as herbal drug. Currently, there is much growing interest to use these medicinal plants as modulators of the complex immune system. Through a number of researches conducted in the area have explored that many of the chemicals in the form of alkaloids, flavonoids, terpenoids, polysaccharides,^[3] lactones, and glycoside products are responsible to cause alterations in the immunomodulatory properties.^[3]

The current research in the area to develop plant-derived natural products as potent and safer leads to act as

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immunomodulators, is gaining much interest. Generation of herbal medicine as multiple-component agent expected to modulate the complex immune process in such a way so as to prevent the infection rather than treatment and cure of the disease. With all these aspects keeping in mind, the present review focuses on an overview of a number of medicinal plants and their immunomodulatory activity.

IMMUNITY

The term immunity defines body's natural defense system against a vast array of diseases and disorders. Remarkably sophisticated and advanced among vertebrates, the complex immune system is capable to generate a limitless variety of cells and molecules to arrest enormous spectrum of infections and undesirable substances. Immunomodulators refer to those substances capable of inducing, amplifying, and inhibiting any component or phase of the immune system. Immunostimulators and immunosuppressant are two types of immunomodulators are known for use. In fact, immunopharmacology is a newer branch of pharmacology concerned with immunomodulators.^[4] Administration of immunostimulators as in the case of AIDS and use of immunosuppressor in cases of an exaggerated response of an immune system is appreciating to reconstitute the normal immune system and increase the longevity of life. Immunomodulator intake along with antigen, the process is meant to boost the immune system, and the modulator is known as immune adjuvant.^[5]

Immunology is one of the rapidly developing fields of biomedical research, holds great promises concerning various diseases and disorders. The two ways of defense of an immune mechanism involving short-term mechanism which is the first line of defense and the other highly advanced adaptive immune response marked by complexity, diversity, and memory.^[6] An adaptive immune response also consists of two subtypes of immune responses, humoral immune response concerned with β -lymphocytes and cell-mediated cytotoxic response mediated by T-cells.^[6] Well, all the component cells of the immune system originate from bone marrow through hematopoiesis from bone marrow-derived stem cells. They are either develop into mature cells or migrate to other peripheral sites for migration.^[6] Besides a vast range of specialized cells of immune cells, certain molecules called cytokines which are one of the important mediators of the immune system mediate the cross talk between the specialized cells of the immune system, thereby completely integrating the behavior and action responses of the cells.^[7]

CYTOKINE MODULATION CAUSED BY HERBAL PLANTS

Through a number of *in vitro* and *in vivo* studies conducted to see the effect of the herbal medicine on cytokines have shown

that they influence a large number of multiple cytokines. By nature, cytokines are a group of soluble extracellular proteins or glycoproteins in the form of interleukins (ILs), interferons, chemokines, etc., and are crucial to both innate and acquired types of immunity. These cytokines through intermolecular cross talks maintain physiological stability through their secretions in all nucleated cells through inducible response to some injury.^[7] In fact, it is evident from knowledge of the medical literature of various diseases that these disease conditions are in connect with cytokine secretions. In diseases of the central nervous system, these cytokines have a predominant role as in the variety of psychiatric disorders, and abnormal secretions of these chemicals have been demonstrated. Various neurochemicals, neuroendocrine, and neuroimmune substances have appeared at the command of cytokines. Their role has been marked in cases of depression,^[8] Alzheimer's disease,^[9] and schizophrenia,^[10] various behavioral shifts, positive and negative emotions, stress, infection, etc., have all been demonstrated to stimulate cytokine secretion.^[11]

It is apparent from the vast literature on cardiovascular diseases and the role of cytokines as these are abundantly prevalent in the liver, heart, vessels, adipose tissues, etc., and these tissues contribute to inflammatory nature of cardiovascular diseases. Growing realization of the fact, the usefulness of cytokines, roles, alterations in cytokine expression, and targeting their receptors may offer a novel approach to their use as a therapeutic target. A number of pharmacological agents are needed in the form of an antagonist, agonist, and initiator at stimulation. Interferon agonist has been approached by the Food and Drug Administration in the year 1986, for hairy cell leukemia.^[12] Similarly, for rheumatoid arthritis treatment, antigens of tumor necrosis factor- α (TNF- α) have been approached as target.^[13] In periodontal diseases, IL-1 β and TNF- α have been targeted.^[14] Inhibition of TH cell-derived cytokines, use of IL-2 and IL-12, and TNF- α also provide potential benefits therapeutically in neuroblastomas.^[9] Cytokines manifest diverse and pleiotropic characters, play a promising role also for other disorders not related to immune system.^[15] The use of interferon produces flu-like symptoms, depression, fatigue, etc., in patients.^[16]

All these hurdles in the way of therapeutic protocol make a challenge for cytokines. Adverse effects produced and experienced among the patients made us consider phytotherapy in modifying the cytokine expression. Plants such as *Astragalus membranaceus* also known as "spleen chi tonic" is a Chinese plant used in various diseases and wasting state of the body. The root extract of the plant was found to lower IL-6 in *in vitro* human model.^[17] IL-6 is inflammatory and impending deterioration marker.^[17] Very well-known plant of garlic or *Allium sativum* used in most of the Indian houses is found to lower IL-1 and IL-6, acting as anti-inflammatory, hypocholesterolemic, antioxidant, and also angiotensin-converting enzyme inhibitor.^[18] It has

great potential as anti-inflammatory due to an inhibitory effect on IL-1, IL-6, TNF, IL-8 and boosting effect on IL-10 which is an antagonist to pro-inflammatory cytokines.^[18] Besides anti-inflammatory, it also manifests antimicrobial potential. Garlic use has been suggested in inflammatory bowel diseases. Its use is also indicated in Alzheimer's disease due to IL-10 modulation. Spelman *et al.* have reported in his review, immunomodulatory activity of more than 18 herbal plants including *Acanthopanax gracilistylus*, *A. sativum*, *Ananas comosus*, *Cissampelos sympodioides*, *Coriolus versicolor*, *Curcuma longa*, *Tinospora cordifolia*, and *Withania somnifera*.^[19] Aloe vera, a very popular plant which grows in arid climate, is claimed to have wound and burn healing properties due to its anti-inflammatory nature. It has been found to reduce TNF- α and IL-6 in various animal models.^[20]

EFFECT OF MEDICINAL PLANTS ON INNATE AND ACQUIRED IMMUNE COMPONENTS

Various herbal medicines have been found to modulate various components of innate and acquired immune system. In fact, based on proper understanding of various immunomodulatory activities of herbal plants, plants derived the secondary metabolites in natural products can be the lead molecules for the future development of immunomodulators for therapeutic use. Various immunomodulators have been suggested in various allergic diseases including asthma, allergic rhinitis, and eosinophilic esophagitis on the basis of experiments performed on various animal models.

EFFECT ON INNATE IMMUNE SYSTEM

Although most of these products are not up to the mark in the human trial, which warrants for the careful understanding of the mechanism of various phenotypes with the goal to decrease excessive TH2 cells through blocking critical TH2 cytokines activity. Inhibition of cytokine involved in the synthesis of TH2 cells, blocking TH2 effector molecules, and inhibition of various cell types involved in TH2 induction.^[21] Assessment of plant activity should be conducted against immunoglobulin E (IgE) (main effector molecule in allergic response), for targeting IL-4/IL-13 receptors and for hiking in the ratio of TH1/TH2 balance. These aforesaid sites are promising targets for immunomodulatory therapy in allergic reactions.^[22] Halwani R, *et al.* have reported the reduction in eosinophil infiltration of lungs and inhibition of airway hyperresponsiveness among ovalbumin level of IgE and associated cytokines IL-5, IL-4, and IL-13 when they were treated with *Ganoderma lucidum*, *Glycyrrhiza uralensis*, and *S. flavescens*.^[23] Components of innate immunity involved in immunomodulation are array of cells including natural killer (NK) cells, NKT-cells, T-cells, macrophages, granulocytes (neutrophils, eosinophils, and basophils), and dendritic cells while B-cells naïve CD4+ T-cells, differentiated CD4+

T-cells including helper T-cells (TH1, TH2, and TH17 cells), induced regulatory T-cells, and natural regulatory T-cells.^[24]

EFFECT ON ACQUIRED IMMUNE SYSTEM

Patil *et al.* explained that ethanolic extract of *Ficus carica* produces stimulatory effect on humoral and cell-mediated immune response in experimental animals and suggested its therapeutic use in immunological disorders.^[25] *Chlorophytum borivillianum* root extract, an effective immunomodulator, not only potentiates non-specific immune response but also improves humoral as well as cell-mediated immunity. It may use in infection condition, enhancement of immunological response against foreign particles or antigens, and improving defensive response under normal circumstances.^[26] Ethanolic extract and aqueous extract of *Picrorhiza kurroa* have the ability to stimulate humoral response by acting various level of immune mechanism such as antibody production, release of mediators of hypersensitivity reactions, and tissue responses to these mediators in the target organs.^[27]

CURRENT DEVELOPMENTS IN IMMUNOMODULATOR RESEARCH

From historical times, through all ages, plants-based medicines have been frequently used in the treatment and prevention of diseases. In fact, researchers are attracted toward plants-based therapeutics. The current research is based on the search for some plant biochemicals in the form of the single compound which is like lead molecule concerned with particular target linked with disease. To transform this lead molecule with least toxicity and maximum selectivity and potency with respect to its target, its further design and development through chemical modification to make it therapeutically fit is nowadays gaining much interest. There are a number of medicines derived from plants such as vinblastine, vincristine, *Madagascar periwinkle*, capsaicin from chili pepper, and paclitaxel from Pacific yew while few chemically altered lead molecules derived from plants are dicoumarol (warfarin), artemisinin (artemether), camptothecin (irinotecan and topotecan), morphine, and salicylic acid (acetylsalicylic acid). Plant-derived chemicals in the form of terpenoids, steroids, phenolics, flavonoids, etc., are all manifesting worth mentioning immunomodulatory activities. In India, more than 70% of the total population is dependent on non-allopathic system of medicine, namely, Ayurvedic, Yoga, Unani, Siddha, Homeopathy, and Naturopathy which also maximally use herbal drugs as a tool to treatment. Hence, these systems of medicines are not mere folklore or traditional herbal practices, but there is some basis established to logically prescribe the herbal drugs.

The term "Reverse Pharmacology" for the first time being proposed by Vaidya to understand the mechanisms of action of herbal drugs at multiple levels and to optimize safety, efficacy, and acceptability of the leads from natural products, based

on relevant science. With expanding knowledge of herbal therapeutics, newer pharmacophores may evolve for new targets with an involvement of unique innovative techniques. The contribution of combinatorial chemistry in search for a novel pharmacophore using varied chemical modifications and optimizations of the herbal lead molecule is appreciating. Curcumin or Haldi in Indian parlance has been chemically modified and optimized to have drug candidate with efficient efficacy and therapeutic action using combinatorial chemistry approach. Various drug research concerns in India are working in the direction to detect the novel activities of plant-derived products. A number of herbal-based projects looking for formulation for diabetes, arthritis, malaria, cancer, etc., are running at global level under the Council for Scientific and Industrial Research. Industries are working on medicinal plants in collaboration with academia and government bodies in the direction. However, despite a huge amount of work done, so far, no systemic review or database is available in our country. Even there is no proper mention of our work which is published in Indian journals and in international databases. This study suggests for revision of the work done in varied fields such as ethnobotany, phytochemistry, pharmacology, and pharmacognosy at the global level.

Some future suggestions and developments are desirable and worthy of consideration:

- Improvement of the study design of clinical studies to establish herbal drug safely for therapeutic use.
- International cooperation and pooling of research data from different parts of the world.
- Reinforcement of target-based approach using newer innovative techniques to identify the lead molecule.
- More and more research should be focused on existing herbal products to remove therapeutic dilemma.

CONCLUSION

Many of the chemicals in the form of alkaloids, flavonoids, terpenoids, polysaccharides, lactones, and glycoside products are responsible to cause alterations in the immunomodulatory properties.

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