A Review on Role and Mechanism of Action of Phytoactives of Medicinal Plants in Augmenting 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." Some of the medicinal plants valued in Ayurvedic Rasayana for their therapeutic potential 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. Currently, there is much growing interest in the use of these medicinal plants as modulators of the complex immune system. Hence, this review of literature study was conducted with the main purpose to delineate the role and mechanism of action of phytoactives of medicinal plants in augmentation of immune system. This scientific evidences and comprehensive pharmaco-dynamic knowledge related to medicinal plants could help researchers to design clinical trials. Furthermore, integration of this concept would certainly help to develop the drug therapy in the near future.**

Index Terms **- Augmentation, Cytokine modulation, Immune system, Medicinal plants, Mechanism of action, Phytoactives.**

I.INTRODUCTION

According to the World Health Organization (WHO), about three-quarters of the world population relies upon traditional remedies (mainly herbs) for the health care of its people. In fact, herbs and/or plants are the oldest friends of mankind. They not only provided food and shelter but also served to cure different ailments. Herbal medicine, sometimes called traditional or natural medicine, has always existed in one way or another in different cultures and civilizations, such as Ayurvedic (India), Egyptian, Western, Chinese, Kampo (Japan) and Greco-Arab or Unani-Tibb (south Asia). Traditional medicine all over the world is currently being revalued through extensive research activity on various plant species and their therapeutic properties [1].

Pandemic diseases are of global concern in the present era, to cause gigantic morbidity and transience, regardless of, extensive medical facilities. Particularly, anti-viral therapies have been fraught because of surfacing of mutants competent enough to subdue the drugs targeting viral elements [2]. It is 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 [3]. 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 [4].

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… [4]. 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 research studies conducted in the area have explored that many of the chemicals in the form of alkaloids, flavonoids, terpenoids, polysaccharides, [5] lactones, and glycoside products are responsible to cause alterations in the immunomodulatory properties [5].

The current research in the area to develop plant-derived natural products as potent and safer leads to act as 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. Hence, herbal or medicinal plant formulations could be essential alternative strategy, a step ahead to battle these awful viruses. With these viewpoints, the present review of literature study was conducted to demarcate the role and mechanism of action of phytoactives of medicinal plants in augmentation of immune system.

II. 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 [6]. 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 [7].

III. IMMUNE SYSTEM

The basic architecture of the immune system is multilayered, with defenses on several levels. Most obvious and primary is the skin: the first barrier against infection. Another is physiological, where conditions like the temperature and pH of the body provide inappropriate living conditions for foreign organisms. Once pathogens have successfully entered the body, they are addressed by the innate and/or the acquired or adaptive immune system. Both systems consist of a multitude of cells and molecules that interact in a complex manner to detect and eliminate pathogens. Detection and elimination depend upon chemical bonding: surfaces of immune system cells are covered with various receptors, some of which chemically bind to pathogens, while others bind to other immune system cells or molecules to enable the complex signaling system that mediates the immune response [8].

IV. IMMUNE SYSTEM BOOSTING THROUGH CYTOKINE MODULATION

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 [9]. 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 [10], Alzheimer's disease [11], and schizophrenia [12]; various behavioral shifts, positive and negative emotions, stress, infection, etc., have all been demonstrated to stimulate cytokine secretion [13].

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 [14]. Similarly, for rheumatoid arthritis treatment, antigens of tumor necrosis factor-α (TNF-α) have been approached as target [15] In periodontal diseases, IL-1β and TNF-α have been targeted [16].

Inhibition of TH cell-derived cytokines, use of IL-2 and IL-12, and TNF-α also provide potential benefits therapeutically in neuroblastomas [11]. Cytokines manifest diverse and pleiotropic characters, play a promising role also for other disorders not related to immune system [17]. The use of interferon produces flu-like symptoms, depression, fatigue, etc., in patients [18]. All these hurdles in the way of therapeutic protocol make a challenge for cytokines. Adverse effects produced and experienced among the patients prompted to 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 [19]. IL-6 is inflammatory and impending deterioration marker [19]. Very well-known plant of garlic (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 [20]. 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 [20]. 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 their review study that immunomodulatory activity of more than 18 herbal plants including Acanthopanax gracilistylus, A. sativum, Ananas comosus, Cissampelos sympodials, Coriolus versicolor, Curcuma longa, Tinospora cordifolia, and Withania somnifera [21]. 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 [22].

V. INNATE AND ACQUIRED IMMUNE SYSTEM – ROLE OF MEDICINAL PLANTS

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 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.

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 [23].

Assessment of plant activity should be conducted against main effector molecule in allergic response i.e., immunoglobulin E (IgE), 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 [24]. Halwani et al have reported the reduction in eosinophil infiltration of lungs and inhibition of airway hyper responsiveness 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 [25]. 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 [26].

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 [27]. Chlorophytum borivilianum 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 [28]. 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 [29].

VI. MECHANISM OF ACTION OF THE IMMUNOMODULATORS

It has been reported that the "immunomodulators" are rejuvenators, nutritional supplements and possess strong antioxidant activities. They also exert antagonistic action on oxidative stressors, giving rise to the formation of different free radicals. They are used mainly to combat the effects of ageing, atherosclerosis, cancer, diabetes, rheumatoid arthritis, autoimmune disease and Parkinson's disease. The immunomodulatory herbs seem to operate through immunostimulant, immunoadjuvant, and immunosuppressant activities or by affecting the effector arm of the immune response [30]. Mechanisms of immunomodulation activity occur mainly via phagocytosis stimulation, macrophages activation, immunostimulatory effect on peritoneal macrophages, lymphoid cells stimulation, cellular immune function enhancement and nonspecific cellular immune system effect, antigen-specific immunoglobulin production increase, increased nonspecific immunity mediators and natural killer cell numbers, reducing chemotherapy-induced leukopenia, and increasing circulating total white cell counts and interleukin-2 levels [31-33].

Modulation of the immune responses through the stimulatory or suppressive activity of phytoextracts 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 [34]. A high degree of cell proliferation renders bone marrow a sensitive target, especially to various cytotoxic drugs. In fact, bone marrow is the organ most affected during any immunosuppression therapy with this class of drugs. Loss of stem cells and the inability of the bone marrow to regenerate new blood cells results in thrombocytopenia and leucopenia [35]. Saponins are either triterpenoid or steroidal glycosides proven to be essential phytoconstituents with various pharmacological activities, such as antiallergic, anti-inflammatory, cytotoxic, antitumor, antiviral, immunomodulatory, antihepatotoxic, molluscicidal, and antifungal activity. Recently, three diosgenyl saponins isolated from Paris polyphylla have been reported to have immunostimulant properties [36]. Lymphocyte stimulation tests were performed on eight cycloartane-type saponins isolated from Astragalus melanophrurius, [37] to determine the role of saponins in the immunomodulating effect of the plant. Higher concentrations of tested compounds have exhibited inhibitory effects.

Cycloartane and oleanane-type triterpenes from these species have unmistakably induced interleukin-2 activity [38]. Immunomodulatory activities of terpenoid compounds such as glycyrrhizinic acid, ursolic acid, oleanolic acid, and nomilin have been

reported [39]. A novel triterpenoid has been isolated from the root bark of Ailanthus excelsa roxb. (Tree of Heaven), AECHL-1, and has potential as an anticancer agent [40].

Many studies have reported that the identification of immunomodulatory compounds with pharmacological activity and a limited toxicity. In this context, ethnopharmacology represents the most important way possible to uncover interesting and therapeutically helpful molecules. The phytochemical analysis of immunomodulatory 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 [41].

VII. 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.

VIII. CONCLUSION

Many of the phytoactives viz. alkaloids, flavonoids, terpenoids, polysaccharides, lactones, and glycoside are responsible for the augmentation of immune system through modulation of cytokines, innate, and acquired immune system. From the above review it was apparent that there are many medicinal plants which exert immunomodulatory activities 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. This scientific evidences and comprehensive pharmaco-dynamic knowledge related to medicinal plants could help researchers to design clinical trials. Furthermore, integration of this

concept would certainly help to develop the drug therapy in the near future.

IX. FUTURE PERSPECTIVES

The following suggestions and developments are desirable and worthy of consideration in future for the development of ethnomedicines which can save the humankind from various ailments and save the lives during pandemic situations through boosting of human immune system.

- 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.

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