

HERBAL IMMUNO MODULATORS - AN OVERVIEW

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The study of Ethnopharmacology ascribes the launch of numerous drugs into International pharmacopoeia. A significant number of plants used in the traditional system of medicine are believed to promote positive health and maintain organic resistance against infection by establishing the body equilibrium. It is tempting to speculate that the restorative and rejuvenating power of these herbs may be due to their action on the immune system.

The concept of immunomodulation relates to the procedure that can alter the immune system of an organism by interfering with its functions: if it results in an enhancement of immune reactions, it is named as immunostimulative drug which primarily implies stimulation of non specific system i.e. granulocytes, macrophages, complement, certain classes of T-lymphocyte and different effector substances. Immunosuppression implies mainly to reduce resistance against infections, stress and may occur on account of environmental or chemotherapeutic factors (Jayathirtha and Mishra, 2004).

Innate and Adaptive Immune Response

Immune response has evolved to protect the body from infectious agents. In addition, immune response is generated against self-proteins and other molecules in auto immunity and against aberrant cells in tumor immunity. Mechanism of protection against infection and disease are primarily divided into two major categories: Non-specific (**innate**) and specific (**adaptive**).

The faster acting innate immune responses provide a necessary first line of defense because of the relatively slow nature of adaptive immunity which is the second line of defense. Innate immune response, among their many effects lead to a rapid burst of inflammatory cytokines, secretory molecules like transferrin, interferons, lysozyme, fibronectin, and complement and also activation of cellular components such as

neutrophils, macrophages, monocytes, NK cells and K cells. These responses lead to a conditioning of the immune system for subsequent development of specific adaptive immune responses.

Adaptive immune system is a complex and sophisticated system that recognizes the foreign invader, destroy them and retain the memory of the encounter so that on subsequent exposure, the immune system responds more rapidly and effectively. Here, pivotal role is played by the clonal expansion of two classes of lymphocytes viz. T (thymus derived) and B (bone marrow derived) cells assisted by Antigen Presenting Cells (APC) like macrophages, dendritic cells etc. and thereby providing specificity and long lasting immunological memory (Pashine *et al*, 2005). By adaptive immune response, pathogens may elicit humoral (antibody mediated) or/and cell mediated response that is mediated by the effectors T and B lymphocytes, each of which contributes to ridding the host of the pathogen.

The humoral immune response is effective against extra cellular pathogens whereas cell mediated immune response (CMIR) is active against intra cellular pathogens and also for tumor cell destruction. In CMIR, the predominant role is played by T lymphocytes and macrophages. The cell mediated immunity include killer activities by specific and non specific killer cells and also delayed type of hypersensitivity reaction mediated by cytokines produced by activated T helper cells which include monocyte chemotactic factor, IL-2, TNF α etc.

Essential features of adaptive immune response

The specificity of adaptive immune response resides on the T cell receptor (TCR) which recognizes pathogen derived peptides (antigen)

bound to MHC (major histocompatibility complex) molecules which is expressed on antigen presenting cells and also B cell receptor (BCR) that binds antigen on its surface directly. There are two classes of MHC molecules viz. MHC class I and class II. MHC class I is recognized by TCR of CD8 cytotoxic T cells (Tc cells) whereas MHC class II is recognized by TCR of CD4 helper T cells (Th cells). The binding of antigen to the TCR or BCR leads to the specific clonal expansion of either effector T cells or antibody producing plasma cells resulting in antigen elimination.

Among these different component of immune system, macrophages and cytokines act as two main targets of immunomodulatory agents.

Macrophages (Mö)

Mö play a central role in immune system and upon activation they are involved in

- initial defense
- antigen presentation
- effector function

Mö activation can be defined as quantitative alterations in the expression of various gene products by the function of Th1 cells which release IFN α . Bacterial endotoxin can also trigger Mö activation by a combination of IFN α and TNF α . Activated Mö release Tumor Necrosis Factor (TNF), IL-1, IL-6, IL-12, reactive oxygen species (ROS), reactive nitrogen species (RNS) and nitric oxide (NO) to destroy the pathogens.

Cytokines

Cytokines are diverse group of non antibody protein secreted by immune cells and act as messengers of immune systems. They have autocrine and paracrine functions, so that they act locally or at a distance to enhance or suppress immunity.

They can be grouped as

- i) Mediators and regulators of natural immunity which include TNF α , IL-1, chemokines, IFN α , IFN γ , IL-12 and IL-10
- ii) Mediators and regulators of specific immunity like IL-2, IL-10, IL-5, interferon and transforming growth factor (Roitt and Brostoff, 2001).

Herbal immunomodulators

A number of traditional medicinal plants have been identified as promising source of immunomodulators that will have a great deal of interest in enhancing the immune functions. One of the main strategies in

Ayurvedic medicine is to increase body's natural resistance to the disease or stress causing agent rather than directly neutralizing the agent itself in practice. The immunomodulatory therapy could provide an alternative to conventional chemotherapy to a variety of diseased conditions. Study on the active principles and mode of action of traditional medicines may contribute to a better understanding of their mode of action at molecular levels. Thus it may also help to evaluate the therapeutic efficacy, to maintain herbal quality and to develop novel drugs.

Among the large array of herbal immunomodulators identified, only few are scientifically validated using different experimental models. Some of those proven immunomodulatory plants and their mechanism are as follows

◀ An aqueous extract of the bark, leaf, and seed of *Azadirachta indica* (Neem) showed an increase in phagocytic activity and induced expression of MHC II antigens on macrophages indicating enhancement of antigenic potency, stimulated lymphocyte proliferative response of splenocytes to mitogens and selectively activated Th1 type of T cell response (Upadhyaya and Dhawan, 1994).

◀ Syringin and Cordiol isolated from *Tinospora cordifolia* enhanced the humoral and cell mediated immunity dose dependently and an increase in IgG antibody level in serum was also observed. The extract of *T. cordifolia* induced a significant increase in the number of colony forming units of the Granulocyte-Macrophage series (CFU-GM) indicating the activation of Mö leading to leukocytosis and enhanced neutrophil function (Thattai *et al*, 1994).

◀ Suresh and Vasudevan, 1994 reported an enhanced natural killer cell activity and antibody dependant cellular cytotoxicity in mice after administration of aqueous extract of *Phyllanthus emblica*. The alcoholic and aqueous extract of *Embblica* enhanced the humoral and cell mediated immune response as evidenced by the increased globulin concentration in the serum, leukocytosis, enhanced DTH reaction, macrophage migration index, and respiratory burst activity of macrophage indicating macrophage activation (Suja R S, 2003).

◀ Sitoindoside IX and X isolated from *Withania somnifera* showed significant mobilization and activation of peritoneal Mö phagocytosis and increased activity of lysosomal enzymes secreted by the Mö, indicating Mö activation (Ghosal *et al*,

1989).

◀ Mangiferin isolated from *Mangifera indica* induced both in vivo and in vitro activation of peritoneal Mφ. It induced IFN release from the Mφ and showed lymphoproliferative effect and Mono Amine Oxide (MAO) enzyme inhibition from macrophages.

All these findings suggest that immuno modulation is the pharmacological manipulation of immune system and the immuno modulators can enhance or inhibit the immune responsiveness of an organism by interfering with its regulatory mechanism.

Application in veterinary field

Diseases are in fact manifestations of the interaction between the disease causing agents and the immune system of the host. Once the disease is contracted, its outcome is largely determined by the immune competency of the host. Therefore, it would be a better profitable proposition to attempt stimulation of the immune system in the management of disease rather than treating them after getting infected. They also prevent or retard the age related decline seen in immune function. But the dose, timing, route of administration of the immunostimulant and presence of concurrently administrated compounds are important factors that may influence the action of drug-host defense

mechanism. In addition, animal factors such as age, degree of passive immunity, plane of nutrition and the disease process itself, may have an impact on the efficacy of immuno modulator.

Ethnoveterinary medicine offers great potential to the development of low cost, safe and effective alternatives to allopathic medicines. Assessing the pharmacological, physiological and toxicological aspects of herbal medicine will help to reduce the need for large doses of antibiotics, antiparasitic agents, hormones, steroids and other drugs. Besides, the herbs coming under the classes adrenergics, immuno stimulants and tonics can be used to minimize the adverse effects of conventional therapy.

Conclusion:

Recent development in biotechnology has shown that the essential factors for the development of any science are personal and group effort, involvement of interested organization, teaching and training at University level and financial support from government. So, for the successful development and implementation of ethnoveterinary medicine, we require the support at all these mentioned levels.

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