IMMUNOMODULATORS OF PLANT ORIGIN – A REVIEW

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ABSTRACT: The immunomodulatory property of plants is being studied with greater interest in recent years. This is more so because of the growing awareness regarding the need to modulate the immune system to achieve the desirable effects of preventing an infection rather than treating it at an advanced state. The recent advances in this field are summarized in this article.

INTRODUCTION

The basic function of immune system is to detect and destroy the non-self and thus a defence mechanism. The system works throughout the body through an intricate regulation of cellular and humoral factors. Its protective task, starting with the recognition of non-self bodies and substances puts the immune system in a vital position between a healthy and diseased state of the host.

The concept of immunomodulation, in its modern sense, was developed by Lazarev, referring to the non-specific resistance increasing property of diabazol. In recent years, the field of immunomodulation attracted attention from the scientific community, in view of the growing awareness regarding the need to modulate the immune system to achieve the desirable effects of preventing an infection rather than treating it at an advanced state.

IMMUNOMODULATION

An immunomodulator is defined as a biological or non-biological substance that directly influences a specific immune function or modifies one or more components of immunoregulatory network to achieve an indirect effect on a specific immune function.

A number of clinical conditions, like cancer, surgery or administration of drugs are known to affect the different components of the immune system, thereby making the host susceptible to infections. Also, stress, be it physical or psychological, causes immunosuppression. Such are the situations, which call for immunostimulant drugs to boost the immune defences against the host. The result has been the development of the concept of “pro-host therapy” and administering drugs, like glucans, muramyl dipeptide, interleukin-1 and colony stimulating factors, to enhance the non-specific host resistance against infections. However, the major drawbacks of these substances are their prohibitive cost and development of local reactions like granuloma formation.

As opposed to the need for immunostimulants, there also are cases of immune-hypersensitivity reactions, such as asthma, autoimmunity, graft rejection, arthritis, allergy and inflammatory disorders, in which an immuno-suppressor is indicated. Most of such agents in clinical
use are the cytotoxic drugs such as azathioprine\textsuperscript{17}, cyclophosphamide\textsuperscript{18}, prostaglandins\textsuperscript{19}, cyclosporine A\textsuperscript{20}, thiacarbomate\textsuperscript{21}, levamisol\textsuperscript{22}, niridazole\textsuperscript{23} and pencillamine\textsuperscript{24}. The main disadvantage of these drugs is their cytotoxicity and associated side effects.

Against this background, the use of herbal drugs, to restore and rejuvenate positive health and to maintain organic balance, has been in vogue since ancient times and the rasayana therapy in Ayurvedic medicine\textsuperscript{25} encompasses many plant preparations which have been used as tonic drugs.

In this paper, an effort has been made to elaborate the current trends in the investigations on the immunomodulators of plant origin.

**IMMUNOMODULATORY STUDIES**

Literature survey shows that there is a spurt in the past few years, in research on immunomodulators of plant origin. A number of plants of known therapeutic properties are evaluated on a battery of experiments to identify their mechanism of action at the molecular level.

Labadie et al evolved the new concepts in ethno-pharmacognosy through basic and field enquiries into the literature and practice of traditional Indian medicine. In the their integrated studies on immunomodulating properties of Azadirachta indica bark, Woodfordia fruticosa flowers, Picrorrhiza kurroa roots and Jatropha multifida latex, the data was collected on ethnobotanical, ethnopharmacological, ethnopharmaceutical and ethnomedical aspects, and the experimental immunopharmacognostic phase was carried out by isolating and purifying compounds through activity-guided fractionation in human complement and PMN leucocyte activation experiments\textsuperscript{26}.

The inhibition of complement activation and luminal-dependent chemiluminescence by *A.indica* was proposed\textsuperscript{27,28}, to be in *in-vitro* correlate of its anti-inflammatory and anti-reumatoidal effects, for which it is widely used. The stimulation of lymphocyte function, as shown by dose-dependent increase in production of migration inhibition factor (MIF), might be an underlying factor in the general stimulating and skin-healing properties of *A.indica*. In the recent studies\textsuperscript{29}, gallic acid, (+)-gallacatechin, (-)-epicatechin, and (+)-catechin were isolated from *A.indica* in activity-guided fractionation studies.

The polysaccharides from the roots of *Panax ginseng* have been used clinically as an anti-tumor drug in China. Recent studies\textsuperscript{30} have revealed that the anti-tumor polysaccharides also have anti-complementary activity and that the polysaccharides from the leaves of *P.ginseng* show higher anti-complementary activity than those from the roots.

The immuno-suppressant property of 5,20-(R)-Dihydroxy-6, 7-epoxy-1-oxo-(5)-with-2, 24-dienolide from *Withania somnifera* and the steroidal alkaloid solasodine from *Solanum nigrum*, in inhibiting the proliferation of spleen cell culture, are supposed to be responsible for the activity of these plants in curing rheumatism, asthma and various skin affections including carbuncles and obstinate ulcers\textsuperscript{31}.

The wound-healing activity of *Aloe vera* leaf-gel was sought to be explained on the basis of the immuno-modulatory activity of the polysaccharide fractions isolated from it\textsuperscript{32,33}. The polysaccharides displayed adjuvant activity on specific antibody
production and the induction of delayed type hypersensitivity in mice\textsuperscript{33}.

Root extract of \textit{Picrorrhiza kurroa} was fractionated on the basis of the inhibition of zymosan-induced chemiluminescence. The components responsible for the activity were indentified to be apocynin, vanillic acid and picroside II\textsuperscript{34}.

The anti-inflammatory activity of \textit{Glycyrrhiza glabra} was found to be due to its constituent glycerrhizin, which acted by significantly inhibiting the generation of reactive oxygen species (ROS) by neutrophils, the most potent inflammatory mediators at the site of inflammation\textsuperscript{35}.

The immuno-modulatory activity of polysaccharides isolated from \textit{Arnica Montana} was revealed in carbon-clearance test and in stimulation of macrophages to excrete tumor necrosis factor\textsuperscript{36}.

The immuno-modulatory activity of \textit{Piper betle} leaves, \textit{Zingiber aramatica} rhizome, \textit{Allium sativum} and \textit{Andrographis paniculata} was displayed by their stimulation of humoral immune response by the “microtitration hematoglutinin test” and suppression of cellular immune response by delayed hypersensitivity test. It was also noted that their water-soluble and water-insoluble portions exhibited opposite results on phagoctytic activity by carbon clearance test\textsuperscript{37}.

The recent trend in evaluation of the immunomodulators of plant origin is towards assessing the activity profile of the isolated principles in a battery of experiments with a view to identify the components responsible for the activity as also to understand the mechanism of their action. Amongst diverse class of compounds, it was observed that flavonol series possess the most potent anti complementary activity\textsuperscript{38}. The \textit{Citrus} flavonoids were found to be very active inhibitions of basophil histamine release and neutrophil β-glucuronidase release, thus exhibiting the \textit{in-vitro} correlate of their anti-allergic and anti-inflammatory activity\textsuperscript{39}. (+)-Dihydroquercetin was found to be a less potent inhibitor of competent activity, compared to that of (+)-catechin, (-) - epicatechin and acetylsalicylic acid\textsuperscript{40}. Flavonoids have exhibited immunostimulant activities too. Flavonie-acenostimulant activities too. Flavonie – acetic acid (FAA), a C-8 substituted flavone derivative, has been shown to cause significant regression in a variety of murine tumor models, caused significant lymphocyte proliferation as well as increase in phagocytosis of zymosan\textsuperscript{41}. The potent anti-phlogistic and anti-allergic activity of the flavonid Wedelolactone from \textit{Eclipta alba} and \textit{Wedelia calendulaceae} was found to be due to its 5-lipoxygenase inhibitory activity, suggesting that it acts by free oxygen radical scavenger mechanism\textsuperscript{42,43}.

Studies have also accounted for the tonic properties of plants like \textit{A.indica}, \textit{Holarrhena antidysenterica}, \textit{Aconitum heterohyllum}, \textit{Tyllophora asthmatica}, \textit{Ocimum gratissimum} and \textit{Tinospora cordifolia}, in stimulation of lymphocytic and phagocytic function and inhibition of humoral components of the immune system\textsuperscript{44-46}.

In the preliminary studies on the immuno-potentiating action of some Ayurvedic drugs\textsuperscript{47} like \textit{Kanjanara gulgulu}, \textit{Rasa sinduram} and \textit{Khadirarishtam}, administered to cancer patients, it was found that the T-cell count showed a slight enhancement after the treatment.
The significant aspect of the bioavailability of active constituents in traditional preparations was studied in case of the Ayurvedic drug *Nimba arishta*; wherein the flowers of *Woodfordia fructicosa* were found to be important ingredient of *Kalka* (paste), which is added to the decoction of *A.indica*, with respect to the modulation of complement activity\textsuperscript{48}.

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