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## Indian Medicinal Plants: A Rich Source of Natural Immuno-Modulator

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**Abstract:** Immuno-modulators play a key role in immunity of each animal in this world. Almost all animals have their own system to produce different immuno-modulators at different time. This review focuses on the use of a variety of natural products/drugs in the enhancement and suppression of impaired immune system under unfavorable conditions. The main accent of this review is to emphasize on the need to evaluate the potential of Indian Ayurvedic remedies as adjuvants to counteract side effects of modern therapies. This study also highlights on the process involved in drug discovery from plant extracts in India. The review assigned a brief discussion on past and present scenario of herbal medicines in India with some important recommendations, suggestions and future directions in this area of herbal medicines.

**Key words:** Immunomodulator, natural medicine, medicinal plant, therapeutic agent

### INTRODUCTION

Plants are the invaluable, incredible and traditional sources for the curability of various diseases in the form of medicines (Guerra *et al.*, 2003). Plants are the main source of drugs that being used from the ancient times as a herbal remedies for the health care, prevention and cure of various diseases and ailments (Kalia, 2005). Plants secondary metabolites have been implicated for most plants therapeutic activities (Timothy *et al.*, 2008). Drug discovery from plants involves a multidisciplinary approach combining botanical, ethnobotanical, phytochemical and biological techniques. They continue to provide us new chemical entities (lead molecules) for the development of drugs against various pharmacological targets, including cancer, HIV/AIDS, malaria, Alzheimer's disease and pain. Several natural product drugs of plant origin are in clinical use, including paclitaxel, camptothecin-derived analogues, arteether, galanthamine, tiotropium to name a few and some are undergoing Phase II and Phase III clinical trials (Jachak and Saklani, 2007). According to WHO out of 252 drugs which are considered as basic and essential 11% are of plant origin for instances digoxin from *Digitalis* sp., quinine and quinidine from *Cinchona* spp., vincristine and vinblastin from *Catharanthus roseus*, atropine from *Atropa belladonna* and morphine and codeine from

*Papaver somniferu* are quite a lot of illustrations are found. WHO also says that about three quarters of world population depends upon traditional remedies (Ansari and Inamdar, 2010). Plants use as a medicines have not been occurred recently, but its use as a traditional and folklore drug throughout the world for the health services is a matter of tremendous historical legacy and evidences (Hoareau and Dasilva, 1999). Consequently herbal medicines have been used from centuries for safety, efficacy, lesser side effect and cultural acceptability. Accordingly plant and its products are safe and as a result there is continuous use of plant product as a drug is found to be an alternative way to cure the patients and this approach is in practice from the ancient times (Venkat Subramanian *et al.*, 2003). A large population of India is using plants for its healing, preventive, curative and many therapeutic properties together with immunomodulatory property (Ranjith *et al.*, 2008). Out of seventy thousand angiosperm plants, three lakhs are recorded for medicinal purposes by the people of different civilization all over the world (Pushpangadan, 2006). A lot of medicinal plants have some beneficial compounds present in them which are used as functional foods (Tilak *et al.*, 2005, 2006; Devasagayam *et al.*, 2001) for instances garlic ginger, mustard, red chilli, fenugreek (Dixit *et al.*, 2005; Kulkarni *et al.*, 2006). Apart from various therapeutic properties of plants today the most

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emphasis of researchers at present on a variety of immunomodulators which could enhance the immune system and eventually combat the disease or infection by modulating immune responses. Some of the plants with established immunomodulatory activity are *Viscum album*, *Panax ginseng*, *Asparagus racemos*, *Tinospora cordifolia* etc. (Satakopan, 1994). Many fruits like Avocado, are having beneficial effect on immune system along with their minor cytotoxic property may be utilized for making natural immune modulators (Kulkarni *et al.*, 2010).

### PRESENT SCENARIO AND STATUS OF HERBAL MEDICINES IN INDIA

India is found to be a country with rich biodiversity and enormous treasure of herbal plants and consequently called as medicinal garden of the world (Bhutani and Gohil, 2010). Many indigenous system such as Ayurveda, Yoga, Unani, Homeopathy, Naturopathy and Siddha are famous and prevailing in India from decades (Vaidya and Devasagayam, 2007). Texts from Bible and Vedas also portray about the use of herbal remedies (Hoareau and Dasilva, 1999). Ayurveda the most refined literature in different languages such as Sanskrit, Hindi and regional languages describes various medicinal plants and emphasize on strengthening of the host immune system (Agarwal and Singh, 1999). It has also been reported that more than 1200 diseases are mentioned in different classical in Ayurveda (Kumar *et al.*, 2007). Charak Samhita and Sushruta samhita are the two most famous treatises of Ayurveda and several other were compiled over the centuries such as Bela Samhita, Kashyap Samhita, Agnivesh Tantra, Vagbhata's Ashtang hridaya (600), Madhava Nidan (700 A D). Not only this Meteria medica has been reported to use leaves, bark, fruits, flowers etc as plant products for herbal drugs. Sushuruta, vagabha and charak has found to described 700 herbal drugs with their properties and clinical effects. Some examples of ayurvedic formulations that contain ingredients from medicinal plants that have antioxidant property are Liv-52, chapparal, c-phycocinin, amritabindu etc. Apart from this Indian medicinal plants have been used as cosmetics and for neuracitical purposes. For instance *Aloe vera* is found to be a dermato cosmetics and its role in antiaging is still untapped. Clinical and therapeutic uses of many Indian medicinal plants have been recorded (Claeson *et al.*, 2000). It is found that Indian medicinal plants possess antioxidant property immensely and approximately 40% plants show antioxidant property, for instance *Acacia catechu*, *Allium cepa* (onion), *Azadiractha indica*, *Bacopa monniera*, *Withania somnifera*, *Tinospora cordifolia* and so on (Sies, 1996).

As we are knowledgeable about that India is full of medicinal plants showing anticancer, antifungal, anti-inflammatory and many more properties, but due to lack of systematic reviews on the massive work from our nation, its popularity is little low because many international databases and website do not cover the work published in Indian journals (Satakopan, 1994). If we talk about herbal drug industries, it is a very fast growing sector in the international market but India has not up to the mark due to lack of scientific input and approaches in the herbal world (Bhutani and Gohil, 2010). But along with some negative points there are many constructive and convinced approaches are also accountable in Indian system of medicine such as DBT, CSIR and AYUSH along with ministry of health and family welfare have initiated efforts on bioprospecting and the golden triangle partnership between ICMR, CSIR and AYUSH has made efforts for the validation of traditional ayurvedic drugs and development of new drugs (Bhutani and Gohil, 2010; Jachak and Saklani, 2007). Recent research and advancement in India divulge that the starting compound need in synthesis of oseltamivir (drug against tamiflu, HINI virus known as shikimic acid) now also available in high yield in Indian plants such as *Callophyllum apetalum* and *Araucaria excels* can be used as an alternative source of shikimic acid. Nicholas piramal India ltd (NPIL), one of the major pharma players in India has built up a plant extract library having 6000 extracts prepared from around 2300 plant species collected from all over India and such libraries could serve as a powerful tool and source of extracts to be screened for biological activities using high-throughput assays (Jachak and Saklani, 2007). It has also have been reported that by using Reverse pharmacological approach several institutes are carrying clinical research on the potential health benefits of herbal drugs (Vaidya, 2006; Patwardhan *et al.*, 2004).

### IMMUNOMODULATION AND OUR IMMUNE SYSTEM

The immune system comprises of Innate (non-specific) and Adaptive immunity (specific) (Tan and Vanitha, 2004) and other cells like macrophages, natural killer cells. Antigen Presenting Cells (APCs) are involved in the fighting against antigens. These antigens could be (fungi, viruses, bacterial toxin) which are processed by APC's presented to T-cells for further processing. Phagocytic cells which are involved in immune system are neutrophils, basophills, eosinophills and monocytes, they engulf and destroy the antigens or foreign substances with their intra cellular mechanisms (Ranjith *et al.*, 2008).

The first thing done in the field of immunomodulation was the search of immunomodulatory agent for the treatment of residual cancer (Agarwal and Singh, 1999). Cytokines and interferon are used in the immunotherapy of cancer (Nadkarni, 2000). Cytokines are also used as immunoadjuvants along with vaccines. Cyclosporin is a potent immunosuppressant proved to be boon for prevention of graft rejection (Agarwal and Singh, 1999). It is also been in autoimmune diseases. Thus, we can say that the term immunomodulation is a processing of suppressing or stimulating the immune system of the host in order to fight against various diseases and infections (Tan and Vanitha, 2004). The word has from immunology which now in coordination with molecular pharmacology and has resulted into a new study or subject called as immunopharmacology and there has been an immense progress in the field of immunology during last 3-4 decade. In addition, infectious diseases are now primarily considered immunological disorders, while neoplastic diseases and organ transplantation and several autoimmune diseases may involve in an immunosuppressive state (Rinku *et al.*, 2009). Right from the distinction between cellular and humoral arms of immunity and recognition of cell surface phenotypes on T and B cells, we have come a long way in understanding molecular mechanism of immune response. These involve immunoglobulin and T cell receptor gene rearrangements, complexity of the MHC system and its role in antigen presentation and restriction of effector cytotoxic cells etc (Agarwal and Singh, 1999). Commencing this we can say that the immune system is involved in the etiology as well as pathophysiologic mechanisms of many diseases (Muthaliar, 1998). But due to many unfavourable conditions, environment and diseases it becomes weak, enervated and needs an external source or factor which can augment the immune response in order to fight against various diseases. Neem has an excellent property to enhance immune system in cancer patients with its embedded chemical miracles (Paul *et al.*, 2010). Modulation of the immune responses to alleviate the diseases has been of interest for many years (Nadkarni, 2000). Therefore, from a therapeutic point of view immunomodulation refers to a process and a course of action in which an immune response is altered to a desired level.

**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 in order to alleviate the disease has been of interest since many years and the

concept of Indian Rasayana in Ayurveda has similarity with it (Vaghasiya *et al.*, 2010):

- **Immunosuppressant:** These agents suppress the immune response and could be used for the control of pathological immune response in autoimmune diseases, graft rejections etc
- **Immunostimulants:** These agents are envisaged to enhance body's resistance against infections, they enhance the basal levels of immune response and in individuals with impairment of immune response as immunotherapeutic agent

### NATURAL IMMUNOMODULATORS

There has been remarkable advances in the field of basic immunology during last three to four decades. Immunology is thus probably one of the most rapidly developing areas of biomedical research and has great promises with regard to the prevention and treatment of a wide range of disorders (Plaeger, 2003). The use of plant products as immunostimulants or immunosuppressants has a traditional history and the use of natural products with curative and remedial properties is as ancient as human civilisation and, for a long time, mineral, plant and animal products were the main sources of drugs (Rates, 2001; De Pasquale, 1984). From the ancient times treatment of many diseases were done by modulating the immune system or function by using medicinal plants and their products, this was also the fundamental principle of therapeutic approach (Ismail and Asad, 2009). The present scenario also says that natural compounds can be lead compounds, allowing the design and rational planning of new drugs, biomimetic synthesis development and the discovery of new therapeutic properties not yet attributed to known compounds (Hamburger and Hostettmann, 1991). The main target of the immunomodulatory plant products is primarily their action on the macrophages which play a key role in the generation of an immune response. The therapeutic potential of immunomodulatory agents from plant products and the Ayurvedic concepts of preventive health care have been highlighted by many researchers (Dahanukar *et al.*, 2000). Scientists have described about the clues which can lead to the development of immunostimulatory agents (Dahanukar *et al.*, 2000). In addition, compounds such as muscarine, physostigmine, cannabinoids, yohimbine, forskolin, colchicines and phorbol esters, all obtained from plants, are important tools used in pharmacological, physiological and biochemical studies (Williamson *et al.*, 1996). This is a good sign of advancement and

tremendous progress that in recent years, there has been growing interest in alternative therapies and the therapeutic use of natural products, especially those derived from plants (Goldfrank *et al.*, 1982).

#### Immunomodulatory activity of some crude plant extracts:

It has been tested that Fruits of *Emblica officinalis* (family: Euphorbiaceae) and whole plant of *Evolvulus alsinoides* (family: Convolvulaceae) has been extensively used in Indian Ayurvedic medicine for varieties of medical disorders. The immunomodulatory properties of *Emblica officinalis* and *Evolvulus alsinoides* were evaluated in adjuvant induced arthritic rat model (Ganju *et al.*, 2003). Ethanolic extract of *A. calamus* inhibited proliferation of mitogen (phytohaemagglutinin) and antigen (purified protein derivative) stimulated human peripheral blood mononuclear cells (PBMCs).

In addition, *A. calamus* extract inhibited growth of several cell lines of mouse and human origin. It also inhibited production of nitric oxide (NO), interleukin-2 (IL-2) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). Intracytoplasmic interferon- $\gamma$  (IFN- $\gamma$ ) and expression of cell surface markers, CD16 and

HLA-DR, on human PBMC, were not affected on treatment with *A. calamus* extract but CD25 expression was down regulated (Mehrotra *et al.*, 2003). Crude extract of *Tinospora cordifolia* contained a polyclonal B cell mitogen which enhanced immune response in mice. An arabinogalactan polysaccharide, G1-4A from the stem of *Tinospora cordifolia* examined to modulate induced immunosuppression. Mice pre-treated with G1-4A exhibited protection against lipopolysaccharide (LPS) induced mortality (Desai *et al.*, 2007). Partially purified immunomodulator, G1-4A prevented lipid peroxidation and restored the activities of superoxide dismutase and catalase enzymes. Likewise, oxidative damage, induced by peroxynitrite, was also inhibited by partially purified immunomodulator similar to selective inhibitors of Reactive Oxygen Species (ROS) like mannitol, superoxide dismutase, sodiumazide and antioxidants, GSH and vitamin C (Desai *et al.*, 2002). It also holds anticancer activity too (Singh *et al.*, 2004) Ethanolic extract of *Boerhaavia diffusa*, a plant used in Indian traditional system of medicine, significantly inhibited the cell proliferation (Mungantiwar *et al.*, 1999). Methanolic extract of Avocado fruits enhances lymphocyte proliferation and reduces chromosomal abnormalities produced by cyclophosphamide treatment in cancer patients (Rajkumar *et al.*, 2010). Extracts of *B. diffusa* roots inhibited human NK cell cytotoxicity *in vitro*, production of nitric oxide in mouse macrophage cells, interleukin-2 and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), in human PBMCs. Whereas, intracytoplasmic interferon- $\gamma$  (IFN- $\gamma$ ) and cell

Table 1: List of Plants with Immunostimulatory property

Plants	Common name	Property
<i>Abrus precatorius</i>	Gunja	Immunostimulant
<i>Andrographis paniculata</i>	Kalmegh	Immunostimulant
<i>Aristolochia indica</i>	Isharmul	Immunostimulant
<i>Berberis aristata</i>	Dar-haid	Immunosuppressor
<i>Catharanthus roseus</i>	Sada bahar	Immunostimulant
<i>Clitoris ternatea</i>	Aprajita	Immunostimulant
<i>Cymbopogon martini</i>	Gandh	Immunostimulant
<i>Hyoscyamus niger</i>	Parsikaya	Immunostimulant
<i>Nardostachys jatamansi</i>	Jatamansi	Immunostimulant
<i>Picrorhiza kuruwo</i>	Kutaki	Immunostimulant

surface markers such as CD16, CD25 and HLA-DR did not get affected on treatment with *B. diffusa* extract and demonstrates immunosuppressive potential of *B. diffusa* (Mehrotra *et al.*, 2002). Aqueous leaves extract of biopesticidal plant *Nyctanthes arbor-tristis* has been found as a potent immunomodulator (Puri *et al.*, 1994). Methanol extract of *Eclipta alba* and *Centella asiatica* whole plant showed phagocytic index and antibody titer has been increased significantly. The F ratios of the phagocytic index and WBC count were also significant with a linearity in the dose-response relationship (Jayathirtha and Mishra, 2004). List of some immunostimulant plants are given in Table 1.

#### DRUG DISCOVERY IN INDIA

To obtain isolated active compounds, the plant extracts are first qualitatively analysed by thin layer chromatography (TLC) and/or other chromatographic methods and screened to determine the biological activity or to obtain a general evaluation of biological activities. For purification and isolation, the active plant extracts are sequentially fractionated (Verpoorte, 1989), each fraction and/or pure compound being subjected to bioassay and toxicity evaluation in animals. This strategy is called bioactivity-guided fractionation. After verifying the purity of an isolated active compound, the structure is determined by spectroscopic methods (UV, IR, mass spectrum or NMR) (Verpoorte, 1989). Once the chemical structure is defined, total or partial synthesis and preparation of derivatives and/or analogues can be considered and modulation of the biological activity and definition of the structure-activity relationship can be carried out. After completing all these steps, large-scale isolation (it may necessary to collect the plant again) or partial or total synthesis is required for pharmacological evaluation in pre-clinical, clinical and toxicological trials aimed at future therapeutic use (Hamburger and Hostettmann, 1991). But this approach also requires efficacy and toxicity studies, but these are less time-consuming, as the steps of fractionation, purification and bioassay are basically not required or are far less complex

Table 2: Summary of some Important medicinal plants and their Immunomodulatory Effects

Plant	Chemical compound	Medicinal uses	References
<i>Allium asativum</i>	Organosulfur compounds, extracts	Inhibit growth of tumor, modulate activity of diverse chemical carcinogens, augment macrophages and T lymphocytes and enhanced production of IL-2	Chopra <i>et al.</i> (1958)
<i>Aloe vera</i>	Carboxypeptidase, salicylate, polysaccharides, acemannan, oligosaccharides etc	Anti inflammatory, immunostimulating effect, immunosuppressive, help in antibody production and induction of delayed type hypersensitivity.	Chithra <i>et al.</i> (1998)
<i>Andrographis paniculata</i>	Ethanol extract, purified andrographolides.	Stimulation of antibody DTH macrophages migration, phagocytosis of 14C labeled E.coli, inhibits NO production and proliferation of splenic lymphocytes Stimulates.	Puri <i>et al.</i> (1992)
<i>Asparagus racemosus</i>	Extracts	Induces lag in tumour development, inhibits ochratoxin A induced suppression of IL-1, TNF- $\alpha$ and macrophage chemotaxis, induces production of TNF.	Senna <i>et al.</i> (1993)
<i>Azadirachta indica</i>	Oils	Stimulates cytokines, activates immune system	Thatte and Dhanukar (1997)
<i>Curcuma longa</i>	Diferuloylmethane, sodium curcuminat, volatile oil.	Increases mitogenic response of lymphocytes, inhibits NO, show anti-inflammatory activity anti tumour	Ghatak and Basu (1972)
<i>Nyctanthes arbor-tristis</i>	Lipids	Stimulates macrophages migration, stimulates and DTH response I in <i>in vivo</i> studies	Khan <i>et al.</i> (1995)
<i>Ocimum sanctum</i>	Steroids	Inhibits tumour development in mice, enhances survival of viral encephalitis patients	Das <i>et al.</i> (1983)
<i>Panax ginseng</i>	Saponins and steroids	Stimulates T cells proliferation, augments NK cells, enhances phagocytosis, chemotaxis, production of cytokines	Singh <i>et al.</i> (1984)
<i>Phyllanthus embilica</i>	Vitamin C	Enhances NK cells and ADCC activity against dalton's lymphomascites tumor	Suresh and Vasudevan (1994)
<i>Tinospora cordifolia</i>	Syringen, cordial	Immunomodulatory property	Thatte and Dahanukar (1998)

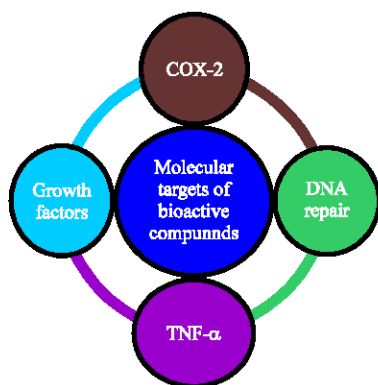


Fig. 1: Various targets of plant active components

Figure 1 shows various targets of plant active components and a list of plants with their active components and immunomodulatory properties in Table 2.

### CONCLUSION

This study has given an overview of importance of different medicinal plants and natural remedies and also clears that immunomodulation using medicinal plants 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 disorders (Ganju *et al.*, 2003). But more

importantly there is a need to evaluate several medicinal plants for their immunomodulatory property which are still unrevealed. With this future suggestions and progress along with simultaneous clinical trials and standardization should be the primary and important steps in pharmacognosy. Different tests should also be performed for the evaluation of immunomodulators for instances immunosuppressant activity, immunostimulatory activity, immunoadjuvant activity and effector arm of the immune response (Agarwal and Singh, 1999). There is also a need to develop and screen plant extracts libraries along with semi synthetic modifications existing hits to get better lead compounds from the natural products (Bhutani and Gohil, 2010). Since India is one of the 12 leading biodiversity and sitting on a gold mine of well recorded and well practiced knowledge of traditional herbal medicine so India can have a great role to play as a supplier of herbal products not only to meet domestic needs but also takes advantages of tremendous export potential. Innovative strategies to improve the process of plant collection, bioassay screening, compound isolation and compound development must be employed (Jachak and Saklani, 2007). In order to get more accurate results, the ayurvedic medicinal formulation prepared on the basis of Materica and medica and rasayans should be go for clinical trials and simultaneously appropriate animal models of disease are developed to evaluate the safety and efficacy (Agarwal and Singh, 1999). In all we can say that there are many great potential for the discovery of more specific immunomodulators from Indian medicinal plants.

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