



A SHORT REVIEW ON PHARMACOLOGY OF PLANT IMMUNOMODULATORS

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Accepted on: 25-04-2011; Finalized on: 25-07-2011.

ABSTRACT

The immunomodulators or *Rasayana's* (in Ayurveda) are agents used to modulate the immune system and can be obtained from both natural as well as synthetic origin from plants and chemicals respectively. The aim of this review is to highlight the work on pharmacological aspects of plant immunomodulators and also provides the knowledge on the recent pharmacological research update in current year (2011). Plants explained in this review having potential of immunomodulating activity are identified from various sources in the literature. Among these many plants have undergone *in vitro* as well as *in vivo* evaluations which are explained in this review including the dose administered of particular plant extract and the mechanism involved in immunomodulation.

Keywords: Immunomodulators, Plant extracts, Immunity.

INTRODUCTION

Immunity: It refers to the ability of the body to identify and resist microorganisms that are potentially harmful. This ability enables the body to fight or prevent infectious disease and inhibit tissue and organ damage. The immune system is not confined to any one part of the body. Immune stem cells, formed in the bone marrow, may remain in the bone marrow until maturation or migrate to different body sites for maturation. After maturation, most immune cells circulate into the body and exert specific effects. The immune system has two distinct, but overlapping, mechanisms which help to fight invading organisms:

- Cell-mediated defences (cellular immunity)
- Antibody-mediated defences (humoral immunity)

Cell-mediated immunity (CMI): It is the result of the activity of many leukocyte actions, reactions, interactions that range from simple to complex. This type of immunity is dependent on the actions of the T (Thymus) lymphocytes, which are responsible for a delayed type of immune response. The T lymphocyte becomes sensitized by its first contact with a specific antigen.

Humoral immunity: In humoral immunity special lymphocytes (white blood cells), called B (Bone cell) lymphocytes, produce circulating antibodies to act against a foreign substance. This type of immunity is based on the antigen-antibody response.¹

Immune system: The architecture of the immune system is multi-layered, with defences on several levels. Most elementary is the skin, which is the first barrier to infection. Another barrier is physiological, where conditions such as pH and temperature provide inappropriate living conditions for foreign organisms. Once pathogens enter the body, they deal with the innate immune system and 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. Both detection and elimination depend upon chemical bonding: surfaces of immune system cells are covered with various receptors, some of which chemically bind to pathogens and some of which bind to other immune system cells or molecules to enable the complex system of signaling that mediates the immune response.

Innate immune system: The term "innate" refers to that part of the immune system with which we are born; that is, it does not change or adapt to specific pathogens (unlike the adaptive immune system). The innate immune system provides a rapid first line of defence, to keep early infection in check, giving the adaptive immune system time to build up a more specific response. Innate immunity consists primarily of a chemical response system called complement, and the endocytic and phagocytic systems, which involve roaming "scavenger" cells, such as macrophages, that detect and engulf extracellular molecules and materials, clearing the system of both debris and pathogens.

Adaptive immune system: The adaptive immune system is so-called because it adapts or "learns" to recognize specific kinds of pathogens, and retains a "memory" of them for speeding up future responses. The learning occurs during a primary response to a kind of pathogen not encountered before by the immune system. The primary response is slow, often first only becoming apparent several days after the initial infection, and taking up to three weeks to clear an infection. After the primary response clears an infection, the immune system retains a memory of the kind of pathogen that caused the infection. Should the body be infected again by the same kind of pathogen, the immune system does not have to re-learn to recognize the pathogens, because it "remembers" their specific appearance, and will mount a



much more rapid and efficient secondary response. The secondary response is often quick enough so that there are no clinical indications of a re-infection. Immune memory can confer protection up to the life-time of the organism (measles is a good example in this regard). The adaptive immune system primarily consists of certain types of white blood cells, called lymphocytes, which circulate around the body via the blood and lymph systems.²

Immunomodulators: It may be defined as a substance, biological or synthetic, which can stimulate, suppress or modulate any of the immune system including both innate and adaptive arms of the immune response.

Classification of immunomodulators: In clinical perspective immunomodulators can be classified into following three categories.

Immunoadjuvants: These agents are used for enhancing efficacy of vaccines and, therefore, could be considered specific immune stimulants³. One of the best known example is Freund's adjuvant⁴. The immunoadjuvants hold the promise of being the true modulators of immune response. It has proposed to exploit them for selecting between cellular and humoral, Th1 (helper T1 cells) and Th2, immunoprotective and immunodestructive, and reagenic (IgE) versus immunoglobulin G (IgG) type of immune responses, which poses to be a real challenge to vaccine designers³.

Immunostimulants: According to definition these agents are inherently non-specific in nature as they envisaged enhancing body's resistance against infection. They can act through innate immune response and through adaptive immune response. In healthy individuals the immunostimulants are expected to serve as prophylactic and promoter agents i.e. as immunopotentiators by enhancing basic level of immune response, and in the individual with impairment of immune response as immunotherapeutic agents⁵.

Immunosuppressants: These are a structurally and functionally heterogeneous group of drugs, which are often concomitantly administered in combination regimens to treat organ transplant rejection and autoimmune diseases⁶.

Methods for testing immunological factors⁷

The routine process for screening is to extract single ingredient or single distilled fraction from herbal drugs, determine its bioactivity by the classic pharmacological means. The whole animal model is the most classic pharmacological screening model, which is very important at the aspect of medicine evaluation because it can apparently respond to the efficacy, side effect and toxicity of medicines in whole. Although this method is high cost and low efficient, at present it is still a primary way to drug discovery and evaluation. Several *in vitro*, *in vivo* methods of pharmacological screening of medicinal plants having immunomodulatory activity has been listed below:

In vitro methods:

1. Inhibition of histamine release from mast cells
2. Mitogen induced lymphocyte proliferation
3. Inhibition of T cell proliferation
4. Chemiluminescence in macrophages
5. PFC (plaque forming colony) test *in vitro*
6. Inhibition of dihydro-orotate dehydrogenase

In vivo methods:

1. Spontaneous autoimmune diseases in animals
2. Acute systemic anaphylaxis in rats
3. Anti-anaphylactic activity (Schultz-Dale reaction)
4. Passive cutaneous anaphylaxis
5. Arthus type immediate hypersensitivity
6. Delayed type hypersensitivity
7. Reversed passive arthus reaction
8. Adjuvant arthritis in rats
9. Collagen type II induced arthritis in rats
10. Proteoglycan-induced progressive polyarthritis in mice
11. Experimental autoimmune thyroiditis
12. Coxsackievirus B3-induced myocarditis
13. Porcine cardiac myosin-induced autoimmune myocarditis in rats
14. Experimental allergic encephalomyelitis
15. Acute graft versus host disease (GVHD) in rats
16. Influence on SLE-like disorder in MRL/lpr mice
17. Prevention of experimentally induced myasthenia gravis in rats
18. Glomerulonephritis induced by antibasement membrane antibody in rats
19. Auto-immune uveitis in rats
20. Inhibition of allogenic transplant rejection

Pharmacology of immunomodulatory plants

There is an excessive need for understanding plant based drug immunological profile, administration and dosage, since high doses tend to be immunosuppressive and low doses of the same tend to become immunostimulatory. Finally it should be noted that most *in vitro* or *in vivo* models are not adequate or not simple enough to ensure that the same can be used as a drug. Many phytoconstituents from plants like polysaccharides is considered to be biological response modifiers and have been reported to enhance various immune responses, such as complement activation, proliferation of lymphocytes and stimulation of macrophages. The



immunopharmacological activities of phenolics are complex and are still not completely understood. Findings *in vitro* do not always agree with observations *in vivo*. Moreover, the effects of different flavonoids may be antagonistic; in some cases they are immunosuppressive and in others, immunostimulatory. Numerous flavonoids have been seen to influence the function of enzyme systems that are critically involved in the immune

response, and in the generation of inflammatory processes, especially in the transduction of cellular activation signals⁸⁻²². Pharmacological aspects of some immunomodulatory plants have been discussed below and also the recent pharmacological research update on plant immunomodulators in current year (2011) have been discussed in Table 1.

Table 1: Recent pharmacological research update on plant immunomodulators in current year (2011)²³⁻³⁷

Plant/family name	Common name	Part used	Dose (mg/kg)	Extract	Phytoconstituents	<i>In vitro/in vivo</i> model	Result of study
<i>Chlorophytum borivilianum</i> , Liliaceae	Safed musli	Roots	2 g/kg	Aqueous	Polysaccharides	HA	Polysaccharides caused significant stimulation of NK cell activity and hence played promising role in modulating immune function
<i>Pinus radiata</i> , Pinaceae	Monterey pine	Bark	5, 10, 20	Proanthocyanidin-rich extract (PAE)	Proanthocyanidins	Proliferation of peripheral blood mononuclear cells in specific pathogen-free White Leghorn chickens	PAE significantly promoted the expression of T helper 1 cytokine (interferon- γ) and decreased the expression of T helper 2 cytokine (IL-6)
<i>Ficus bengalensis</i> , Moraceae	Banyan tree	Roots	200-400	Aqueous	Phenolics	DTH, HA, Total leukocyte count Differential leukocyte count	Higher dose (400 mg/kg) of aqueous extract showed statistically significant immune modulatory activity
<i>Tridax procumbens</i> , Asteraceae	Coat button	Whole aerial parts	2, 4	Chloroform, ethyl acetate, <i>n</i> -butanol	Phenolics	HA, Neutrophil adhesion	Isolated compounds showed dose relative immunostimulatory effect on <i>in vivo</i> immune functions in mice
<i>Epilobium angustifolium</i> , Onagraceae	Fireweed	Flowers	5–20 μ g/ml	Methanolic, Oenothien B compound	Oenothien B (dimeric hydrolysable tannin)	Chemotaxis assay, Cytokine analysis, Analysis of NF- κ B activation, Cytotoxicity assay	Oenothien B modulated phagocyte functions <i>in vitro</i> and <i>in vivo</i>
<i>Actinidia kolomikta</i> , Actinidiaceae	Kiwi	Roots	2.5-25 μ g/ml	Hydro-alcoholic	Polysaccharide	Activation assay, Measurement of nitric oxide production, Phagocytosis assay, Cell cycle analysis	Crude polysaccharide fraction stimulated macrophage proliferation, nitric oxide production and phagocytosis in a dose-dependent manner
<i>Tecoma undulate</i> , Bignoniaceae	Rohida tree	Bark	100	Ethanollic	Flavonoids, phenolic compounds	HA	Ethanollic extract produced stimulatory effect on the humoral and cell mediated immune response in the experimental animals and suggested its therapeutic usefulness in disorder of immunological origin
<i>Hordeum vulgare</i> , Poaceae	Pearl barley	Grass	0.1-0.4 mg/mL	Fiber containing fractions	Arabinoxylan	NF- κ B activity assay, Complement fixing test	High molecular weight mixed-linked β -glucans from barley were active in the complement-fixing test but had not affect proliferation and secretion of IL-8 of the colon epithelial cell lines Caco-2 and HT-29, or NF- κ B activity in the monocytic cell line
<i>Aloe vera</i> , Liliaceae	Aloe	Leaves	100	Saline	Alkaloids	HA	Extract suppressed delayed type hypersensitivity reaction induced by SRBCs in mice as evidenced by marked increased in haemagglutination titers in mice
<i>Ocimum sanctum</i> , Lamiaceae	Tulsi	Entire plant	100, 200	Aqueous	Flavonoids, terpenoids	Passive haemagglutination assay (Chromic chloride method)	Aqueous extract showed increased antibody production in dose dependent manner and enhanced the production of RBC, WBC and haemoglobin
<i>Solanum xanthocarpum</i> , Solanaceae	Yellow-berried nightshade	Fruits	100	Methanolic	Alkaloids, phenolics	Neutrophil adhesion test, Hematological test	Methanol extracts of fruits showed pronounced immunoprotective activity by increasing the depleted levels of total WBC count, RBC, % Hb, % neutrophils adhesion
<i>Cudrania tricuspidata</i> , Moraceae	Silkworm thorn	Roots	-	Aqueous	Polysaccharides	Mitogen induced lymphocyte proliferation	Polysaccharides stimulated the proliferation of mouse spleenocytes and also enhanced pinocytic activity of mouse peritoneal macrophages
<i>Ganoderma microsporium</i> , Ganodermataceae	Hemlock	Fruiting body	-	Immunomodulatory protein (GMI)	Immunomodulatory protein	Cell viability assay	GMI induced lung cancer cell death by activating autophagy but had not induced apoptotic cell death
<i>Berberis lycium</i> , Berberidaceae	Barberry	Entire plant	0,25,20,22.5 g/kg	<i>B. lycium</i> extract	-	Antibody titre against (infectious bursal disease IBD) and new castle disease (ND)	<i>B. lycium</i> added to feed at 20 g/kg was effective in improving immunity against ND and IBD as well as liver function in broiler chicks
<i>Panax ginseng</i> , Araliaceae	Ninjin	Entire plant	10,50,100 μ g	Ginsenoside Rg1	Ginsenoside Rg1	Mitogen induced lymphocyte proliferation	Results showed that the groups immunized with rSAG1(recombinant surface antigen) and Rg1 (50 μ g, 100 μ g) developed a high level of specific antibody responses against <i>T. gondii</i> rSAG1, a strong lymphoproliferative response, and significant levels of cytokine production, compared with the other groups

1. *Citrus natsudaoidai* Hayata (Family: Rutaceae): The modifying effects of auraptene isolated from the peel of citrus fruit (*C. natsudaoidai* Hayata) on macrophage and lymphocyte functions were investigated on mice. Female BALB/c (Bagg Albino) mice were gavaged with auraptene at a dose of 100, 200 or 400 mg/kg once a day for 10 consecutive days. Auraptene did not enhance spontaneous IL-4 (interlukin-4) production by splenocytes. There was no significant difference in IL-4 production of splenic lymphocytes stimulated by concanavalin A in all groups. These findings suggested that oral administration of *C. auraptene* effectively enhanced macrophage and lymphocyte functions in mice⁸.
2. *Allium hirtifolium* Boiss. (Family: Alliaceae): Hydroalcoholic extract and polyphenolic fraction of *A. hirtifolium* significantly reduced footpad thickness in immunomodulatory models. These findings suggested that both hydroalcoholic extract and polyphenolic fraction of *A. hirtifolium* decreased acquired immunity response in a dose-dependent manner. However, only polyphenolic fraction of *A. hirtifolium* showed a dose-dependent effect on intrinsic immunity⁹.
3. *Randia dumetorum* Lamk. (Family: Rubiaceae): The effects of *R. dumetorum* on cell mediated and humoral components of the immune system in mice were observed. Administration of chloroform fraction at dose 100 mg/kg produced statistically significant results as evidenced by increase in humoral antibody (HA) titre, delayed type hypersensitivity (DTH) response. This fraction also enhanced the total WBC (white blood cells) level in cyclophosphamide induced myelosuppression model at dose 100 mg/kg. Petroleum ether fraction and methanol fraction affected only cell mediated immunity¹⁰.
4. *Cleome gynandra* Linn. (Family: Capperdiceae): The assay of immunomodulatory activity of ethanolic extracts of aerial parts of *C. gynandra* Linn. (50, 100 and 200 mg/kg, p.o.) was done by carbon clearance method for non-specific immunity, haemagglutination antibody titre method for humoral immunity and footpad swelling method for cell mediated immunity on wistar albino rats. Ethanolic extract of *C. gynandra* Linn. exhibited significant immunosuppression effect in dose dependent manner when compared with control group¹¹.
5. *Andrographis paniculata* Nees (Family: Acanthaceae): Alcoholic extract of plant exerted a strong immunomodulatory effect along with isolated andrographolide. Both are able to induce significant stimulation of both 'antigen specific' and 'antigen nonspecific' types of immune responses in mice, showing effectiveness against a variety of infectious and oncogenic (cancer causing) agents¹².
6. *Tinospora cordifolia* Miers. (Family: Menispermaceae): The water and methanolic extract of stem of *T. cordifolia* inhibited immunosuppression caused by cyclophosphamide. The immunobiological activity of ethanolic extract was investigated on delayed type hypersensitivity, humoral responses to sheep RBC's skin allograft rejection and phagocytic activity of reticuloendothelial system in mice¹³.
7. *Bauhinia variegata* Linn. (Family: Caesalpiniaceae): The effect of ethanolic extract of stem bark of *B. variegata* on the primary and secondary antibody responses were evaluated by humoral antibody response for a specific immune response. The effect of ethanolic extract was evaluated by carbon clearance test and neutrophil adhesion test at a dose of 250-500 mg/kg/p.o and the results suggested the potential of this plant as source of immunomodulator¹⁴.
8. *Ganoderma lucidum* (Fr.) P. Karst. (Family: Polyporaceae): Immunostimulatory effects of polysaccharide fraction isolated from plant were tested on induction of cytokine (Tumor necrosis factor- α , interferon- γ) synthesis in primary cultures of human mononuclear cells (PBMC) isolated from a buffy coat. Results have shown the potential of isolated fraction to induce moderate amounts of TNF- α and IFN- γ (interferon- γ) in trace amounts respectively¹⁵.
9. *Alternanthera tenella* Colla (Family: Amaranthaceae): Aqueous extracts of *A. tenella* were investigated *in vivo*. Animals were immunized *in vivo* with sheep red blood cells and concomitantly inoculated intraperitoneally (i.p.) with each extract (50, 100 or 200 mg/kg). Specific antibody-producing cells were enumerated using plaque-forming cell assays (PFC) and anti-SRBC IgG and IgM serum levels were measured via enzyme-linked immunosorbent assay. Body and lymphoid organ weights were determined after treatments in order to evaluate toxic effects. Immunostimulatory activity through modulation of B lymphocyte functions was achieved using aqueous extracts of *A. Tenella*¹⁶.
10. *Acacia catechu* Willd. (Family: Leguminosae): The immunomodulatory effect of aqueous extract of plant was studied at two doses of 5 mg/kg and 50 mg/kg orally. The effect was studied in neutrophil adhesion test, mice lethality test, carbon clearance assay, cyclophosphamide induced neutropenia, serum immunoglobulin levels and the haemagglutination test. *A. catechu* extract produced a significant increase in the serum immunoglobulin levels, increase in the haemagglutination titre values and decreased the mortality ratio in mice, suggesting its effect on the humoral arm of the immune system¹⁷.
11. *Allium hirtifolium* Boiss. (Family: Alliaceae): To study the effects of *A. hirtifolium* on acquired immunity,



groups of Balb/c (Bagg Albino) mice were used. Sheep red blood cell (SRBC) was injected and 5 days later hydroalcoholic extract (10-2000 mg/kg) and polyphenolic fraction (100-1000 mg/kg), betamethasone (4 mg/kg) or normal saline were given ip. After 1 h SRBC was injected to footpad and footpad swelling was measured up to 72 h. To see the effects of *A. hirtifolium* on intrinsic immunity the same procedure was used, Hydroalcoholic extract and polyphenolic fraction of *A. hirtifolium* significantly reduced footpad thickness in both models. These findings showed that both hydroalcoholic extract and polyphenolic fraction of *A. hirtifolium* decreased acquired immunity response in a dose-dependent manner. However, only polyphenolic fraction of *A. hirtifolium* showed a dose-dependent effect on intrinsic immunity¹⁸.

12. *Gymnema sylvestre* R.Br. (Family: Asclepiadaceae): *G. sylvestre* leaves was investigated for immunomodulatory activity by assessing Neutrophil locomotion and chemotaxis test, phagocytosis of killed *Candida albicans* and Nitroblue terazolium tests. The extract was gave at doses of 25 µg/ml, 50µg/ml and 100µg/ml. Results of *in-vitro* immunomodulatory activity lead to the concluded that the aqueous extract of plant showed predominantly significant activity on *in-vitro* human neutrophils in all parameters, which is compared to the standard¹⁹.
13. *Urena lobata* Linn. (Family: Malvaceae): Different concentrations (5-100µg/ml) of methanolic extract were subjected for its immunomodulatory activity using human blood by phagocytosis. The study revealed that the methanolic extract of *U. lobata* Linn. showed phagocytosis and intracellular killing potency of human neutrophils at different concentration²⁰.
14. *Claviceps purpurea* (Fr.) Tul. (Family: Clavicipitaceae): Immunomodulatory activity of isolated ergot alkaloid glycosides (elymoclavine and 9, 10-dihydrolysergol) and their glycosylated derivatives on natural killer (NK) cell-mediated cytotoxicity of human resting and activated human peripheral blood mononuclear cells (PBMC) was investigated. Addition of ergot alkaloid glycosides to the mixtures of effector and target cells potentiated the PBMC cytotoxicity against both NK-sensitive and resistant target cells. The glycoconjugates of elymoclavine enhanced cytotoxicity of PBMC against NK-resistant target cells. The glycoconjugates of DH-lysergol potentiated NK cytotoxicity of PBMC against NK-sensitive target cells²¹.
15. *Allium sativum* L. (Family: Liliaceae): Plant extract inhibited the growth of tumour, modulate activity of diverse chemical carcinogens, augment macrophages and T lymphocytes and enhanced production of IL-2²².

CONCLUSION

From this discussion it is evident that there are many medicinal plants which exert immunomodulatory effect in experimental models at a particular dose. Different types of *in vivo* and *in vitro* screening methods have been employed in determining their pharmacological activity. Some medicinal plants may stimulate the immune system like *Ocimum sanctum*, *Tinospora cordifolia* and some of them may suppress the immune responses example *Alternanthera tenella*. The review also reveals an update of the current immunomodulator plants and their pharmacological aspects in the year 2011. Thus successful results have been achieved by following an appropriate screening approach.

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