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Immunomodulatory effects of some traditional medicinal plants

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ABSTRACT

The Immune System is the most complex biological systems in the body. At the time of infection immune system go under the attack of a large number of viruses, bacteria and fungi. The immune system is a part of body to detect the pathogen by using a specific receptor to produce immediately response by the activation of immune components cells, cytokines, chemokines and also release of inflammatory mediator. They modulate and potentiate the immune system. Medicinal plants impart significant roles in the prevention of human being from various pathogenic microorganisms and the diseases. In nature there are various medicinal plants which are used as immunomodulator agents. This review is an attempt to put various plants in one place which are used as immunomodulatory agents.

Keywords: Immune system, Immunomodulators, T-cells, Cytokines, Chemokines.

INTRODUCTION

The immune system is designed to protect the host from invading pathogens and to eliminate disease. [1] The primary object in the past has been to suppress immune system to permit allotransplantation. Activation of immune system by “non-self” antigen (alloantigen) or “self” antigen (auto antigen) is generally believed to require processing of the antigen by the phagocytic cells such as macrophages, monocytes, or related cells. [2] There are two types of immune response are occurs in the human body:

I) Innate immune response
II) Adaptive immune response
   a. Humoral immunity
   b. Cellular immunity

I) Innate immune response: The innate immune response is the first line of defense mechanism against physical, biochemical and cellular components.
II) Adaptive immune response:
a) Humoral immunity - Antibody production – killing extracellular organisms.
b) Cell mediated immunity – cytotoxic / killer T-cells – killing virus and tumour cells. [3]

Cellular immunity is expressed as cytotoxicity towards target cells by activation of cytotoxic or "killer" T-cells. The action of the cytotoxic T-cell is also inhibited by adrenocorticosteroids. But the humoral arm of the immune response is responsible for the production of the antibodies; this is carried out by cells derived from the bone marrow (β-cell). [4]

In Indian medicinal literature a large number of plants included to promote the physical mental and defense mechanism in to the body. In other hand a large number of medicinal plants included in Rasayanas have been claimed to possess immunomodulatory activities.

Medicinal plants which are used as immunomodulatory effect to provide alternative potential to conventional chemotherapy for a variety of diseases, especially in relation to host defense mechanism. The use of plant product like polysaccharides, lectins, peptides, flavonoids and tannins has been the immune response or immune system in various *in-vitro* modals. [5]

The immune system is a part of body to detect the pathogen by using a specific receptor to produce immediately response by the activation of immune components cells, cytokines, chemokines and also release of inflammatory mediator. In the innate immune the nature killer cell plays an important role to the defiance against virus-infected and malignant cell to destroy the abnormal cell. [6]

Modification of the immune response by pharmacological agents is most effective in therapy is begun before exposure to the antigen has an opportunity to generate a primary response (pretreatment of allograft recipients). A certain autoimmune diseases, such as rheumatoid arthritis, nephritis, uveitis, thyroiditis, and early stages of insulin dependent diabetes mellitus appear to involve response to auto antigen, a potential role for immunosuppressive drug has been recognized. The drug affecting the immune system is termed as immunomodulatory or adaptigenic. Some repress the system and are value in, for example, preventing rejection of transplanted organs and other are stimulating and can be used to help combat viral infection such as AIDS or assist in the treatment of cancer.[7,8]

The Asteraceae family is the largest flowering plants having immunomodulatory activity. This family consists of about 900 genera and some 13,000 species. Different plants having immunomodulatory activity are listed in table 1. [9]

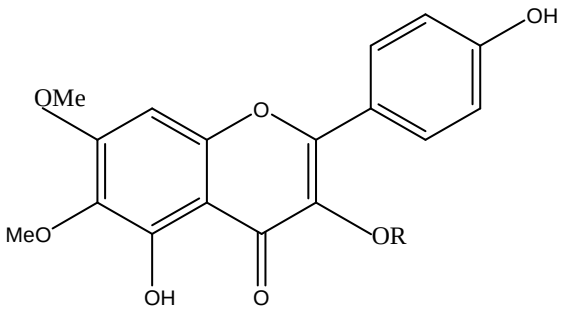
***Boerhaavia diffussa*:-**

Boerhaavia diffusa, (Punarnava; Family Nyctaginaceae), (fig.1) is a creeping weed found abundantly all over India. In Indian traditional medicine, roots of this weed are used for the treatment of dyspepsia, jaundice, enlargement of spleen, abdominal pain and as an antistres agent.

Table-1: List of plants having immunomodulatory activity

S.NO	PLANT NAME	FAMILY	PART USE
1	*Boerhaavia diffussa*	Nyctaginaceae	Root
2	*Curcuma longa*	Zingiberaceae	Rhizome
3	*Rhododendron spiciferum*	Ericaceae	Leaf
4	*Caesalpinia bonducella*	Caesalpiniaceae	Whole plant
5	*Tinospora cordifolia*	Menispermaceae	Whole plant
6	*Capparis zeylanica*	Capparidaceae	Whole plant
7	*Luffa cylindrical*	Cucurbitaceae	seed and fruit (bulb)
8	*Withania somnifera*	Solanaceae	Whole plant
9	*Asparagus racemosus*	Asparagaceae	Root
10	*Panax ginsengs*	Araliaceae	Root
11	*Nelumbo nucifera*	Nymphaeaceae	rhizome and seed
12	*Azadiracta indica*	Meliaceae	Leaf
13	*Arnica montena*	Compositae	Dried flowers head
14	*Calendula officinalis*	Asteraceae	Flower
15	*Echinacea purpurea*	Asteraceae	Flowering top
16	*Euphorbia tirucalli*	Euphorbiaceae	Latex
17	*Ocimum sanctum*	Lamiaceae	Leaf

Fig 1: *Boerhaavia diffusa*



Compounds	R
Bd-I	β-D-galactopyranoside
Bd-II	H

Fig.2

Sita naik *et al*. reported the extraction of *boerhaavia diffussa* in hexane, chloroform & ethanol solvents, they isolated two different compounds i.e. Bd-I (eupalitin-3-O-h-Dgalactopyranoside) and Bd-II (eupalitin) (fig.2) by Flash chromatography.

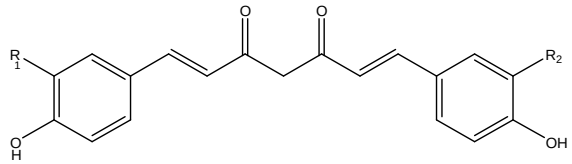
The hexane extract inhibited significantly of PHA-stimulated proliferation of human peripheral blood mononuclear cells at the concentration of 10 μg/ml, while chloroform and ethanol extract give this activity at the concentration of 50 μg/ml. The suppression by Bd-I and Bd-II is dose dependent and ranged from 63–98 % at 500 μg / ml to 7–14 % at 5 μg /ml.

On the other hand the effect of chloroform extract on NK cell is 84% ,ethanolic extract is 48% but the Bd-I & Bd-II is very low i.e. 3% and 12% respectively. [10]

***Curcuma longa*:-**

Curcumin is a main active constituent of *curcuma longa linn* (fig.3) belonging to the family of Zingiberaceae. India is a largest country which produces the *curcuma longa linn* (about 90% of the total output of the world). Curcuma is a genus of about 70 species if rhizomatous herbs distributed in south East Asia especially India, China, Thailand and Malaysia. The curcumin is used for the treatment of anti-inflammatory, antiarthritic, common colds & coughs, jaundice agent.

Fig.3: *Curcuma longa*



Compound	R_1	R_2
Curcumin	OCH_3	OCH_3
Desmethoxycurcumin	OCH_3	H

Fig.4

Gaoa *et al*. was extracted of curcumin (fig.4) in the plant of *curcuma longa*. They have reported that the effect of curcumin on mitogen/antigen induced proliferation of splenic lymphocytes, induction of cytotoxic T-lymphocytes (CTLs), lymphokine activated killer (LAK) cells and the production of cytokines by T-lymphocytes and macrophages. They examine the effect of curcumin on the proliferation of splenic lymphocytes by the 3H-thymidine uptake assay.

Curcumin also inhibited the IL-2 induced proliferation of splenic cells. The inhibition of IL-2 induced proliferation of cells was dose-dependent; since increasing suppressive effect was observed at increasing concentration of curcumin from 6.25 to 25 mmol/L. IL-2 induced proliferation of spleen cells was completely inhibited by curcumin at 25 mmol/L.[11]

Table -2: Effect of curcumin on proliferation (p) of splenic lymphocytes

Compound	Dose	Effect
	6.25 µmol/L	P < 0:001
	12.5 µmol/L	P < 0:0001
Curcumin	25 µmol/L	completely blocked

***Rhododendron spiciferum*:-**

The plant *Rhododendron spiciferum* (fig.5) belonging to the family Ericaceae. They will be widely used as a medicinal plant because of their active constituent's proanthocyanidin A-1 (PAA-1) is highly used for health. Proanthocyanidin A-1 (PPA-1) is used as the free radical scavengers, anti-bacterial agents and effective enzyme inhibitors. They also exhibit the activity of vasodilators, anti-allergic, anti-inflammatory, cardio-protective, immune-stimulating, anti-viral and estrogenic activities.

Fig.5: *Rhododendron spiciferum*

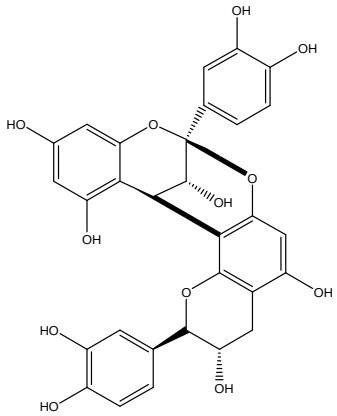


Fig.6. The chemical structure of proanthocyanidin A-1

Y.Z. Liu *et al*., was extracted of rhododendron extract in 70% Acetone, Water, petroleum ether, Ethyl acetate, n-Butanol respectively. They also isolate the proanthocyanidin A-1 (fig.6) in the extract by the column chromatography using Chloroform: Acetone (1:0→6:4) as the eluent to yield five fractions based on silica gel thin layer chromatography (TLC). The fifth fraction of this extract was further applied to the chromatographic by using the solvent Chloroform: Methanol (100:0→40:60) and the isolate of proanthocyanidin A-1.

They have reported that the effect of isolated compound PAA-1 in the cell proliferation is dose dependent i.e. a low dose (5 mg/L) significant effect but the increase of dose the effect will be increase. The effect of this compound in nature killer cell (NK cell) is depend on the concentration i.e. increase concentration (25 mg/L, 50 mg/L , 100 mg/L) will be increase the effect.[12]

Caesalpinia bonducella

Caesalpinia bonducella (fig.7) belonging to the family Caesalpiniaceae. It is commonly known as Nata Karanja. It is indigenous plant of India but also found to be Myanmar, Sri Lanka. The Caesalpinia prickly shrub, globular shaped seeds with a smooth shining surface. The Seeds of these plants consist of a thick, brittle shell with a yellowish white bitter fatty kernel. *Caesalpini bonducella is used the* shows following therapeutic activity like antipyretic, antidiuretic, anthelmintic and antibacterial, anti-anaphylactic and antidiarrheal, antiviral, antiasthmatic, anti-amoebic and anti-estrogenic. In the treatment of liver disorder and tumor, *Caesalpinia bonducella* has been traditionally used.

Fig.7: *Caesalpinia bonducella*

S. Shukla *et al*. was reported that the extraction of *caesalpinia bonducella* by the hot extraction process using the ethanol as a solvent. This extract is used for the activity of immnomodulatory in the mouse. The oral administration of o*caesalpinia bonducella* (ethanolic extract) in the mouse the effect of this is given below. [13]

Table- 3: Phagocytic response of extract in mouse

Compound	Dose	Phagocytic index
Caesalpinia bonducella extract(ethanolic)	200 mg/kg 300mg/kg 400mg/kg 500mg/kg	4.72±0.66, 5.15±0.27, 6.19±0.45 8.13±0.39

Tinospora cordifolia

Tinospora cordifolia (fig.8) belonging to the family of Menispermaceae. This is a perennial climber distributed throughout the tropical Indian subcontinent. It is categorized as in Ayurveda and well known for its adaptogenic and immunomodulatory activity in fighting infection. The activity of this drug appears to be due to alkaloid. The drug shows immunomodulatory activity. It is shown to be effective against various types of experimental induce infection. [14]

Fig.8: *Tinospora cordifolia*

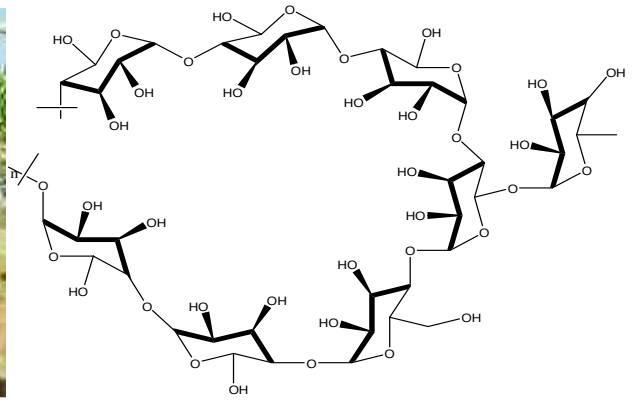


Fig.9

P.K. Raveendran Nair *et al* was isolate of a compound In *Tinospora cordifolia* extract known as a-d-glucan RR1 (fig.9). The hot extraction process which is used for the extraction .In extraction process the methanol, Trichloroacetic acid is used as a solvent .the compound RRA-1 is isolated from this extract by the method of column chromatography & layophilizetion process.

They have reported that the effect of *tinospora cordifolia* extract on the lymphocytic activation. The dose of extract is 100 µg/ml will give the effect of lymphocytic activation i.e. the activation of β-cells is 39%, T-cells 105% and NK cells is 331% respectively . In this result the effect of extract on the NK cells is high,this is a important feature because the NK cells is a important effectors of innate immune system .

RR1 induced the synthesis of IL-1h (1080 pg), IL- 6 (21,833 pg), IL-12 p40 (918.23 pg), IL-12 p70 (50.19 pg), IL-18 (27.47 pg), IFN- g (90.16 pg), MCP-1 (2307 pg) and TNF-a (2225 pg) while it did not induce the production of IL-2, IL-4, IL-10, TNF-h and IFN-a.[15]

Capparis zeylanica

Capparis zeylanica, (fig.10) family: Capparidaceae is commonly known as Indian caper, is a climbing shrub found throughout India and has been used as a 'Rasayana' drug in the traditional in Northern India, the leaves are widely used as counter-irritant, febrifuge and as a cataplasm in swellings, boils and piles. The various species of genus *Capparis* are useful in the treatment of cough, asthma, inflammation, fevers, and cholera and also useful as poultice in gout.

Fig.10: ***capparis zeylanica***

B.V. Ghule et al. was reported that effect of immunomodulatory activity of ethanolic and water extracts of *Capparis zeylanica* leaves. This extract was used to the determination of cellular and humoral immune response using neutrophil adhesion test, phagocytic activity in sheep RBCs. The solvent used for the extraction petroleum ether, ethanol and the processes is hot extraction (soxhletion). A significant ($P < 0.05$) increase in the *in vitro* neutrophil adhesion to nylon fibres by water extract (at a dose of 300 mg/kg, oral). However, ethanolic extract (150–300 mg/kg) do not show any significant increase in neutrophil adhesion. [16]

Nelumbo nucifera

Nelumbo nucifera (fig.11) is a plant belonging to the family of Nymphaeaceae. This plant is a well-known aquatic medicinal plant which has used as a traditional medicine in India. The rhizome extract of Nelumbo nucifera, is used the activity of hypoglycaemic, antidiarrhoeal, antimicrobial, diuretic, antipyretic, psychopharmacological, anti-inflammatory. The seed of this plant is also used for the following activity including anti-ischemic, antioxidant, hepatoprotective, antiproliferative, , anti-inflammatory. The plant contains betulinic acid and a steroidal pentacyclic triterpenoid .The each extract of this plant is used to the immunomodulatory activity.

Fig.11 ***Nelumbo nucifera***

D. Mukherjee *et al*. was reported immunomodulatory effect of the plant extract (Nelumbo nucifera), in Swiss *albino* mice. The extract (NNSE and NNRE) of rhizome and seeds was extracted with 70% ethanol by cold maceration process. They have been reported the activity is dose dependent i.e. the enhancement of NBT (Nitro blue tetrazolium reduction test) reduction was observed more significantly at higher doses of both the extracts, 300 mg/kg (NNSE, $P < 0.001$; NNRE, $P < 0.01$) and than that of their lower dose 100 mg/kg when compared to control 100 mg/kg ($P < 0.01$), 300 mg/kg ($P < 0.001$).

During their study they were observed that adherence of neutrophils to the nylon fiber was increased in both NNRE and NNSE treated groups as compared to the control and concluded that hydro alcoholic extracts of rhizome and seeds of Nelumbo nucifera showed stimulation of defense system by modulating the immunological parameters and shows potential therapeutic benefits of the plant parts on immunomodulation. [17]

Allium sativum

Allium sativum (fig.12) an important medicinal plant having immunomodulatory effects. Three proteins showing immunomodulatory were separated from garlic by Q-Sepharose chromatography of 30 kD ultrafiltrate of raw garlic extract. All these proteins exhibit the mitogenic activity towards human peripheral blood lymphocytes, murine splenocytes and thymocytes.

Fig.12 *Allium sativum*

P.Venkatesh *et al*.,was isolated these immunomodulatory proteins from raw garlic, and examine their effects on the immune system (lymphocytes, mast cells and basophils) in relation to mitogenicity and hypersensitivity.

The extraction of garliac was prepared by blending the bulbs in phosphate buffer saline (ph,7.4). Followed by ammonium sulphate precipitation and were isolated by ultrafiltration , and anion exchange chromatography using Q-Sepharose (High Performance) column taking unbuffered 20 mM 1, 3-diaminopropane taken in 1:10 ratio (w/v), Tris–HCl buffer, pH 8 and NaCl. The eluted fractions were monitored by absorbance at 280 nm.

The richly present garlic ImPs, QR-1 and QR-2, identified in present study as the lectins or agglutinins ASA II and ASA I, was found to be potent mitogenic activity having potential utility in therapeutic immunomodulation. [18, 19]

CONCLUSION

There are a number of natural agents (herbs) which are used for the enhancing of the body's response to disease. In recent time a large number of drugs extracted from the plants are coming in to the market by proper clinical trials. When taking any of these agents take proper advice on dose, length of treatment.

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