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Review Article

A Review on Immune Modulatory Effect of Some Traditional Medicinal Herbs

Sumit Das*, Ripunjoy Bordoloi, Nishant Newar

Girijananda Chowdhury Institute of Pharmaceutical Science, Azara, Guwahati, Assam, India

* **Corresponding author:** Sumit Das **Email:** sumitdas29j@gmail.com

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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 immune modulator agents. Certain medicinal plants are believed to promote positive health and maintain organic resistance against infection by re-establishing body equilibrium and conditioning the body tissues. It is tempting to speculate that the restorative and rejuvenating power of these herbal remedies might be due to their action on the immune system and some of the medicinal plants are believed to enhance the natural resistance of the body to infections. Plant derived materials (proteins, lections, polysaccharides, etc.) have been shown to stimulate the immune system. Ayurveda and other Indian literature mention the use of plants in treatment of various human ailments. There are a number of plants that have been reported to have immune modulatory activity. The present paper review plants which have shown experimental and clinical immune modulatory activity.

Keywords: Immune system, Immuno modulators, T-cells, Cytokines, Chemokines.

INTRODUCTION [1-4]

An immunomodulator may be defined as a substance, biolgical or synthetic, which can stimulate, suppress or modulate any of the components of the immuno system including both innate and adaptive arms of the immune response. Immune system is a remarkably sophisticated defence system within vertebrates, to protect them from invading agents. Modulation of the immune system denotes to

any change in the immune response that can involve induction, expression, amplification or inhibition of any part or phase of the immune response. Thus, immunomodulator is a substance used for its effect on the immune system. There are generally of two types immunomodulators based on their effects: immune suppressants and immune stimulators. Specific immunomodulators administered together with antigens known as immunological adjutants to boost the immune response to the vaccine constituents. For instance, a plant origin saponin used in veterinary medicine. Whereas, the non-specific immunostimulators offer a generalized state of resistance to pathogens or tumors. Fungal product cyclosporin A selectively block the function of T lymphocyte and used to prevent graft rejection. The concept of immunomodulation relates to nonspecific activation of the function and efficiency of macrophages, granulocytes, complement, natural killer cells and lymphocytes and also to the production of various effectors molecules generated by activated cells. It is expected that theses nonspecific effects give protection against different pathogens including bacteria, viruses, fungi etc. and constitute an alternative to conventional chemotherapy. The world we live in is one full of microbes. Our body temperature and wealth of nutrients provide an ideal home for these micro-organisms to thrive. The human immune system has the essential function of protecting the body against the damaging effects of microbial agents that are pathogenic. The system comprises innate (non-specific) and acquired (specific) immunity. Natural killer (NK) cells, complement system, macrophages, antigen presenting cells(APCs) and neutrophils make up the innate immune system and mounts an immediate non-specific response to foreign microbial agents. If microbes by-pass this primary defence, the acquired immune response, comprising humoral and cell mediated components, will then act to contain the invaders. The type of antigen (fungi, virus, bacteria, toxin) processed and presented by APCs to the CD4+ T cell determines the type of cytokines secreted, which in turn, determine the differentiation of helper T (TH) cells into TH1 or TH2 cells and B-cells to give immunoglobulin sub-types. TH1 response involves the activation of macrophages, which contain and destroy mycobacteria and fungal pathogens. TH1 pathway also activates cell-mediated immunity. TH2 cells, on the other hand, effect immunoglobulin differentiation and antibody secretion, and therefore mediate humoral immunity. CD8+ cytotoxic T cells induce apoptosis in antigen-laden cells

CANDIDATE PLANTS OF INDEGENEOUS ORIGIN WITH IMMONOMODULATORY PROPERTIES

Ginseng [5-7]

Synonyms: Ninjin, Pannag, Panax.

Biological source: Ginseng is the dried root of various species of panax like *Panax ginseng* (Korean), *Panax japonica* (Japanese), *Panax notoginseng* (Chinese) and *Panax quinquefolium* (American).

Family: Araliaceae.

Description: *Panax ginseng* belongs to the Araliaceae family and is found throughout East Asia and Russia. It grows natively in remote forests of Manchuria and North Korea, but has become over-harvested in other parts of Asia. It is cultivated in Korea, China, and Japan for export and use as a medicinal herb. *Panax ginseng* is a shade-loving, deciduous perennial with five-fingered leaves, tiny white flowers, red berries, and a yellowish-brown root. The root is utilized medicinally, although active compounds are present in all other parts of the plant.

Active Constituents: *Panax ginseng* contains triterpene glycosides, or saponins, commonly referred to as ginsenosides. Many active compounds can be found in all parts of the plant, including amino acids, alkaloids, phenols, proteins, polypeptides, and vitamins B1 and B2.

Mechanism of Action: *Panax ginseng* is often referred to as an adaptogen, which suggests it has varied actions and effects on the body that support nonspecific resistance to biochemical and physical stressors, improve vitality and longevity, and enhance mental capacity. Reviews suggest *Panax ginseng* has immuno-modulating activity by affecting the hypothalamic-pituitary-adrenal (HPA) axis. *In vitro* experiments reveal enhanced natural killer (NK) cell activity and increased immune cell phagocytosis after ginsenoside exposure.According to a 1999 World Health Organization review, ginseng saponins "are thought to decrease serum prolactin, thereby increasing libido" in male impotence.

Clinical Indications: *Panax ginseng* has been widely studied in double-blind, randomized, placebo-controlled trials (RCTs). Although ginseng has been used by Asian cultures for thousands of years for conditions such as fatigue, mental stress, blood sugar regulation, improving libido, and have focused on the use of *Panax ginseng* in cancer prevention, blood sugar regulation, fatigue, and

immunomodulation in human health and disease.*Immune Modulation*

Drug-Botanical Interactions: According to a review by Blumenthal et al, there are no known interactions between *Panax ginseng* and pharmaceuticals, as reported by the German Commission E. A recent review by Seely et al suggests cautious use of *Panax ginseng* in pregnancy and lactation, although no specific teratogenic or hormone disrupting activity was noted.

Side Effects and Toxicity: *Panax ginseng* is associated with low toxicity; few adverse events have been reported with proper usage. Adverse events have been associated with high doses and long-term usage. Side effects such as hypertension, nausea, diarrhea, headache, mastalgia, insomnia, and skin rash have been noted.

Dosage: Ginseng root can be chewed, or taken as a powder, liquid extract, decoction, or infusion. Crude preparations of 1-2 g dried root powder can be taken daily for up to three months . Dosage of *Panax ginseng* extract standardized to 4-percent ginsenosides is 200 mg per day, in divided doses, yielding 8 mg ginsenosides daily.

Liquorice [8-11]

Synonyms: Glycyrrhiza, Glycyrrhizae radix, Mulethi.

Biolgical source: It consists of dried, peeled, unpeeled, root and stolon of *Glycyrrhiza glabra.*

Family: Leguminosae.

Description: The licorice shrub is a member of the pea family and grows in subtropical climates in rich soil to a height of four or five feet. It has oval leaflets, white to purplish flower clusters, and flat pods. Below ground, the licorice plant has an extensive root system with a main taproot and numerous runners. The main taproot, which is harvested for medicinal use, is soft, fibrous, and has a bright yellow interior.

Active Constituents: A number of components have been isolated from licorice, including a water-soluble, biologically active complex that accounts for 40-50 percent of total dry material weight. This complex is composed of triterpene saponins, flavonoids, polysaccharides, pectins, simple sugars, amino acids, mineral salts, and various other substances. Glycyrrhizin, accounts for the sweet taste of licorice root.

Mechanisms of Action: The beneficial effects of licorice can be attributed to a number of mechanisms. Glycyrrhizin and glycyrrhizic acid have been shown to inhibit growth and cytopathology of numerous RNA and DNA viruses, including hepatitis A9 and C, herpes zoster, HIV,*Herpes simplex*, and Glycyrrhizin and its metabolites inhibit hepatic metabolism of aldosterone and suppress 5-ßreductase, properties responsible for the well-documented pseudoaldosterone syndrome. The similarity in structure of glycyrrhetic acid to the structure of hormones secreted by the adrenal cortex accounts for the mineralocorticoid and glucocorticoid activity of glycyrrhizic acid. Licorice constituents also exhibit steroidlike anti-inflammatory activity, similar to the action of hydrocortisone.

Clinical Indications:

- ***Chronic Hepatitis:*** In Japan, glycyrrhizin has been used for more than 60 years as a treatment for chronic hepatitis C. Stronger Neo-Minophagen C (SNMC), a glycyrrhizin preparation, has been extensively used with considerable success.
- ***Oral Lichen Planus :*** Patients with chronic hepatitis C often experience oral lichen planus, an inflammatory disease characterized by lymphocytic hyperkeratosis of the oral mucosa. It is rarely cured and effective treatments are limited.
- ***Other Viral Illnesses:*** It has been reported that licorice inhibits growth and cytopathology of many unrelated DNA and RNA viruses, while not affecting cell activity or cellular replication. Hepatitis A virus (HAV) causes acute hepatitis, a major public health concern in numerous countries

- ***Hepatocellular Carcinoma:*** In a retrospective study, long-term licorice administration for hepatitis C infection was effective in preventing hepatocellular carcinoma (HCC).

- ***Peptic Ulcer Disease***: Licorice has been used as a demulcent and emollient for 2,000 years to promote the healing of ulcers by acting on the mucosal layer. Glycyrrhizin (as carbenoxolone sodium) speeds healing of gastric ulcers and protects against aspirin-induced damage to the gastric mucosa.

Drug-Botanical Interactions: There is an increased likelihood of cardiac arrhythmias, particularly in individuals with ischemic heart disease, when licorice is used in conjunction with digoxin.65 Estrogen-based oral contraceptives may enhance the mineralocorticoid side effects of licorice in susceptible individuals. This may be due in part to estrogens reacting with mineralocorticoid receptors or inhibition of 11-hydroxysteroid dehydrogenase.

Side Effects and Toxicity: One of the most commonly reported side effects with licorice supplementation is elevated blood pressure. This is thought to be due to the effect of licorice on the renin-angiotensin-aldosterone system. It is suggested licorice saponins are capable of potentiating aldosterone action while binding to mineralocorticoid receptors in the kidneys. The phenomenonighttime pain is known as "pseudoaldosteronism." In addition to hypertension, patients may experience hypokalemia (potassium loss) and sodium retention, resulting in edema. All symptoms usually disappear with discontinuation of therapy.

Dosage: A daily oral intake of 1-10 mg of glycyrrhizin, which corresponds to 1-5 g licorice (2% glycyrrhizin), has been estimated to be a safe dose for most healthy adults.69 Studies of DGL for peptic ulcers employed dosages ranging from 760-2,280 mg DGL daily.

Ginger [12, 13]

Synonyms: Zingiber, Zingiberis.

Biological source: Ginger consists of rhizomes of *Zingiber officinale.*

Family: Zingiberaceae.

Description : Ginger, the rhizome of *Zingiber officinale*, is one of the most widely used species of the ginger family (*Zingiberaceae*) and is a common condiment for various foods and beverages. Ginger has a long history of medicinal use dating back 2,500 years in China and India for conditions such as headaches, nausea, rheumatism, and colds.It is said to be native of South East Asia, but is cultivated in Carribean islands, Africa,Australia, Jamaica, Taiwan and India.

Active Constituents: Ginger contains a number of pungent constituents and active ingredients. Steam distillation of powdered ginger produces ginger oil,which contains a high proportion of sesquiterpene hydrocarbons,predominantly zingiberene.The major pungent compounds in ginger, from studies of the lipophilic rhizome extracts, have yielded potentially active gingerols, which can be converted to shogaols, zingerone, and paradol.4 The compound 6-gingerol appears to be responsible for its characteristic taste. Zingerone and shogaols are found in small amounts in fresh ginger and in larger amounts in dried or extracted products.

Mechanisms of Action: The mechanism underlying ginger's anti-emetic activity is not clearly understood, but the aromatic, spasmolytic, carminative, and absorbent properties of ginger suggest it has direct effects on the gastrointestinal tract. Studies do not indicate ginger has influence within the vestibular

or oculomotor system. A mechanism involving the central nervous system cannot be ruled out, considering several of ginger's components antagonize serotonin type-3 receptors; however, this has not been clearly demonstrated. The compounds 6-gingerol and 6-shogaol have been shown to have a number of pharmacological activities, including antipyretic, analgesic, antitussive and hypotensive effects.

Clinical Indications: It is used in the treatment of Motion Sicknes, Nausea and Vomiting in Pregnancy, Post- surgical Nausea, Chemotherapy-induced Nausea, and Osteoarthritis.

Drug-Botanical Interactions: No drug interactions are known; however, due to ginger's apparent effect on platelets, it should be used cautiously in individuals using anticoagulants.

Side Effects and Toxicity: Ginger is on the U. S. Food and Drug Administration's GRAS (generally recognized as safe) list. *The British Herbal Compendium* documents no adverse effects of ginger.

Dosage: For most purposes a typical dose of ginger is 1-4 g daily, taken in divided doses. To prevent motion sickness, it is best to begin treatment1-2 days before the scheduled trip and continue dosing throughout the duration of travel. For nausea and vomiting during pregnancy, ginger tea made from fresh ginger root,boiled and diluted to taste, appears to work best.

Ashwagandha [14-17]

Synonyms: Withania root, Asgandh, Winter cherry.

Biological source: It consists of dried roots and stem bases of *Withania somnifera*.

Family: Solanaceae.

Description: It grows as a stout shrub that reaches a height of 170 cm (5.6 ft),and also grows widely in all dry parts and subtropical India.It bears yellow flowers and red fruit, though its fruit is berry-like in size and shape. Ashwagandha grows prolifically in India, Nepal, Pakistan, Sri Lanka and Bangladesh. It is commercially cultivated in Madhya Pradesh. (a state in India).

Active constituents: The main constituents of ashwagandha are alkaloids and steroidal lactones. Among the various alkaloids, withanine is the main constituent. The other alkaloids are somniferine, somnine, somniferinine, withananine, pseudo-withanine, tropine, pseudo-tropine, cuscohygrine, anferine and anhydrine. Two acyl steryl glucoside viz. sitoindoside VII and sitoindoside VIII have been isolated from root. The leaves contain steroidal lactones, which are commonly called withanolides. The withanolides have C28 steroidal nucleus with C9 side chain, having six membered lactone rings.

Mechanism action: Ashwagandha is reported to have anti-carcinogenic effects in animal and cell cultures by decreasing the expression of nuclear factor-kappaB, suppressing intercellular tumor necrosis factor, and potentiating apoptotic signalling in cancerous cell lines.

Clinical Indications: Fruits, leaves and seeds of the Indian medicinal plant *Withania somnifera* have been traditionally used for the Ayurvedic system as aphrodisiacs, diuretics and for treating memory loss. The Japanese patent applications are related to the use of the herb as a skin ointment and for promoting reproductive fertility. The U.S based company Natreon has also obtained a patent for an Ashwagandha extract. Another US establishment, the New England Deaconess Hospital, has taken a patent on an Ashwagandha formulation claimed to alleviate symptoms associated with arthritis. The product called "ashwagandha oil" is a combination of ashwagandha with almond oil and rose water designed to be used as a facial toner, and should not be consumed orally.

Drug-Botanical Interactions: No clinical trials of drug or supplement interaction were identified. Animal trials however reported that ashwagandha promoted the activity of phenobarbitone sodium after intra peritoneal administration.

Side Effects and Toxicity: *Withania somnifera* stimulates the thyroid leading to thyreotoxicosis in some humans and in mice.

Astragalus [18-20]:

Synonyms: Milk-vetchroot, Ogi.

Biological source: It is obtained from the dried roots from 4-7 year old plants of Astragalus membranaceus.

Family: Leguminosae.

Description: *Astragalus membranaceus* (Latin*);* membranous milk-vetch root (English), huang qi (Chinese), ogi (Japanese) and hwanggi (Korean) is one of the important “Qi tonifying” adaptogenic herbs from the Chinese materia medica.

Active Constituents: The main constituents of *Astragalus membranaceus* include polysaccharides, saponins, flavonoids, amino acids, and trace elements.

Mechanisms of Action: Research shows Astragalus root stimulates the immune system in many ways. It have been identified as glucans, and polysaccharide D as a hetero polysaccharide increases the number of stem cells in bone marrow and lymph tissue and encourages their development into active immune cells. It appears to help trigger immune cells from a “resting” state into heightened activity. One study showed Astragalus root helps promote and maintain respiratory health. It also enhances the body’s production of immunoglobulin and stimulates macrophages. Astragalus can help activate T-cells and natural killer (NK) cells. Several studies also show Astragalus proffers heart-protecting effects, including protection against oxidative damage

Clinical Indications: Current Western applications of Astragalus are primarily for restoring and strengthening the immune response, enhancing cardiovascular function, and increasing vitality.

Indications supported by clinical trials include impaired immunity, adjunctive cancer treatment, and viral infections, including the common cold and cervical erosion associated with *Herpes simplex*. Astragalus is an effective treatment for leukopenia.19 Astragalus has also been shown to possess *in vitro* antibacterial activity against *Shigella dysenteriae, Streptococcus hemolyticus, Diplococcus pneumonia and Staphylococcus aureus.*

Drug-Botanical Interactions: Recombinant interleukin-2 can be potentiated 10-fold by Astragalus extract. Recombinant interferon-1 can be therapeutically enhanced by Astragalus, thus improving the outcome in chronic viral cervicitis. There is speculation Astragalus could theoretically offset or minimize the immunosuppressive effects of corticosteroids and cyclosporine, based on its T-cell stimulating activity.

Dosage and Toxicity: Astragalus is safe; doses as high as 100 g/kg of raw herb have been given by lavage to rats with no adverse effects.1 Astragalus can be given in tincture form at 2-4 mL three times daily. The LD50 of Astragalus in mice was determined to be approximately 40 g/kg when administered by intraperitoneal injection.

Table 1. Some Marketed Formulations of Immunomodulatory Drug [21]

HIZENTRA	Human normal immunoglobulin (SCIg)	Replacement therapy in adults and children in primary immune-deficiency syndromes suchas:- congenital agammaglobulinaemia and hypogammaglobulinaemia– common variable immuno-deficiency- severe combined immunodeficiency.	14/04/2011	CSL Behring GmbH
FLEBOGAMMA DIF	Human normal Immunoglobulin	Replacement therapy in Primary immunodeficiency syndromes such as congenital agammaglobulinaemia and hypogammaglobulinaemia- common variable immunodeficiency - severe combined immunodeficiency. Immunomodulation in: Idiopathic thrombocytopenic purpura (ITP), in children or adults at high risk of bleeding or prior to surgery to correct the platelet count.	23/07/2007	Bristol-Myers Squibb Pharma EEIG
ORENCIA	Abatacept (INN)	In combination with methotrexate, for the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis (JIA) in paediatric patients 6 years of age and older who	31/03/2009	Intercell AG

		have had an insufficient response to other DMARDs including at least one TNF inhibitor.		
IXIARO	Japanese Encephalitis Vaccine (inactivated, adsorbed)	For active immunization against Japanese encephalitis for adults.	08/09/2003	Abbott Laboratories Ltd.
HUMIRA	Adalimumab (INN)	In combination with methotrexate for the treatment of active polyarticular juvenile idiopathic arthritis, in adolescents aged 4 to 17 years who have had an inadequate response to one or more disease modifying anti-rheumatic drugs (DMARDs) .As monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate Humira has not been studied in children aged less than 4 years.	08/09/2003	Abbott Laboratories Ltd.

CONCLUSION

Allopathic drugs are available for counteracting the oxidative stress and hence improve immunity, but the side effects and prohibitive cost of these allopathic drugs makes it necessary to search for an alternative. The Ayurvedic system of medicines not only provides that alternative, but also scores over the side effectsand cost factor of allopathic medicine Immunomodulators are becoming very popular.

From the work cited in the work it can be concluded that herbals/botanicals have usefulness in the treatment of disease like immunomodulator or which may develops to other immune disorders.Ayurvedic drugs have promising profile as far as drug development from natural source is concerned.One can expect herbal to acts as lead compound for development of economical ,effective and nontoxic immunomodulatory agent.

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