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Phytopharmaceuticals Used as Immunomodulator: An Overview

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Abstract: ***Immunomodulatory therapy is often needed under conditions of impaired immune response and when the immune system's mechanisms should work. Although conventional immunomodulatory chemotherapy treatment is found to be costly and often not affordable for ordinary people with low socioeconomic status, so the transformation of the immune system with traditional herbal products has become the subject of current scientific research worldwide. A large number of medicinal plants have been shown in ancient Siddha literature regarding the management of a number of diseases that lead to immunodeficiency. H Some of the medicinal plants with Ayurvedic Rasayana medicinal properties have been scientifically investigated and yielding promising results. Several plant - based rules have been separated by a strong immune function that can explain and explain its use in traditional medicine in the past and may form the basis for further research in the future as well. The purpose of this review is to highlight the results of research conducted on immunomodulators of plant origin. Paper selection was made using the most relevant biomedical science database on the basis of its ethnopharmacological applications. Many plants and other phytoconstituents that are responsible for immunomodulation have been described. The review also discusses biological testing methods for various herbal medicines that focus on revealing the mechanism involved in immune defense. This work will hopefully encourage researchers to do more work on therapeutic plants with potent immunomodulatory function.***

Keywords: Immune Response, Classification, Immunological Factors, Plants Derived Immunomodulators, Immunomodulatory Activity.

1. Introduction

According to the World Health Organization (WHO), about three quarters of the world's population rely on traditional remedies (especially remedies) for the health care of their people. In fact, herbs and / or plants are the oldest friends of mankind. Not only did they provide food and shelter but they also helped cure various ailments. Herbal medicine, sometimes called traditional or natural medicine, has been present in some way in various cultures and cultures, such as Ayurvedic (India), Egypt, Western, Chinese, Kampo (Japan) and Greco - Arab or Unani - Tibb (southern Asia).

Immunity

This can be described as the body's ability to detect and resist large numbers of infectious and potentially harmful viruses, enabling the body to prevent or resist infections and to prevent organ and tissue damage. The immune system is not limited to any part of the body. Stem cells, located in the bone marrow, may remain in the bone marrow until they mature or move to various parts of the body to grow. Later, more body cellsit circulates throughout the body, producing certain effects. The immune system has two distinct but complementary mechanisms against invasion, the antibody - mediated immune system (humoral immunity) and the cell - mediated immune system (cell defense). [1]

Immune System

The basic structure of the immune system has many layers, defending itself on several levels. The most obvious and main is the skin: the first barrier against infection. Another physiological, in which conditions such as body temperature and pH contribute to unfavorable living conditions of foreign organisms. Once the virus has successfully entered the body, it is directed by the innate and / or acquired or mutated immune system. Both systems contain a host of cells and molecules that interact in a complex way to detect and eliminate viruses. Discovery and termination depend on chemical synthesis: the upper layers of immune cells are covered by various receptors, some of which bind to chemicals in cells, while others bind to other immune cells or molecules to form a complex signaling system that mediates immune responses. [2]

Immunomodulators

These are biological or synthetic substances that can stimulate, suppress or repair any part of the immune system, including both the flexible and innate arms of the immune system.

Classification of immunomodulator: immunomodulators can be classified into the following three categories:

ImmunoadjuvantsThey are used to improve the effectiveness of vaccines and therefore can be considered as a protective stimulant. Immunoadjuvants hold promise to be true modulators of the immune response. It has been suggested that they be used as a choice between T1 (Th1) and helper T2 helper (Th2), immunoprotective, immunodestructive, and reagenic [immunoglobulin E (IgE)] against IgG - type immune responses that pose a real vaccine challenge. designers. [3]

Immunostimulantsthey are not as natural in nature as they are thought to be immune enhancers. They can work by birth and flexible immune responses. In healthy people, immunostimulants are expected to act as prophylactic agents and stimulants, that is, as immunopotentiators, by improving the basic immune response. In a person with an immune response, they are expected to act as immunotherapeutic agents. [4]

Immunosuppressantsare a group of systematic and effective drugs, which are often administered simultaneously with a variety of drugs to treat various types of organ transplants and autoimmune diseases. [5]

Drugs that Modify the Immune Response

Immunomodulatory drugs are Disease Modifying Drugs (DMDs). These are mainly classified into two groups

a) Immunostimulants

1) Synthetic compounds
   E. g. Isonosine, Levamisole.
2) Immune globulin
3) Cytokines
4) E. g. interferon (INF - α), Interleukins (IL - 2) Peptides
   E. g. dialyzable leukocyte extracts, neuropeptides, thymic factors.
5) Microorganisms
   E. g. Basillus Calmette - Guerin (BCG), Muramyl dipeptides, Streptococcal components, Nocardia Components, pseudomonas components and Salmonella components [6].

b) Immunosuppressant

1) Specific T - cell inhibitors (calcineurin inhibitors)
   E. g. cyclosporine, tacrolimus
2) Cytotoxic drugs (Antiproliferative drugs)
   E. g. Azathioprine, Cyclophosphamide, methotraxate, chlorambucil, mycophenolatemofetil.
3) Glucocortcoids E. g. Prednisolone and others.
4) Antibodies. E. g. Muromonal CD3, antithymocyteglobulin, Rho (D) immunoglobulin [7]

Methods for Testing Immunological Factors

A common experimental procedure is to extract a single ingredient or a fraction of a distilled herbal medicine, determining its bioactivity by traditional pharmacological methods. The whole animal model is a very old model of drug testing, which is very important in the field of drug testing because it can obviously respond to the effectiveness, side effects and toxicity of drugs as a whole. Although this method is expensive and very effective, it is still the main method of drug detection and testing. Several in vitro, in vivo clinical trials of medicinal plants with immunomodulatory function have been listed [8].

***In vitro* methods:**

1) Inhibition of histamine release from mast cells
2) Mitogens 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) Arthurs type immediate hypersensitivity
6) Delayed type hypersensitivity
7) Reversed passive Arthurs 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
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.

How medicinal plants can help immune system?

Plants are rich in flavonoids, vitamin C, or carotenoids and can therefore improve body function. Flavor - rich herbs may have little anti - inflammatory action. Their beneficial effect is termed as anti - inflammatory and immune action. It can improve lymphocyte function, increase phagocytosis, and trigger interferon production. For example, garlic is one of the most important herbs that can make the immune system booster available to boost the immune system by stimulating the activity of natural killer cells. For examples some studies strongly suggest that garlic is a promising candidate as an immune modifier, which maintains the homeostasis of immune functions [9] because it contains a large number of sulfur compounds responsible for its therapeutic effects. The chemical components of garlic have also been found in the treatment of cancer, diabetes, atherosclerosis and hyperlipidemia [10].

Table1: A brief description of common plants derived immunomodulators [11 - 41]

Botanical (Family)	Ayurvedic/ Common name	Part used	Chemical constituents	Other biological activities
Ocimum sanctum Linn. (Labiateae)	Tulasi	Entire plant	Essential oils such as eugenol, cavacrol, derivatives of ursolic acid, apigenin	Carminative, stomachic, antispasmodic, Anti - asthmatic, hepatoprotective.
Aloe vera Tourn. ex Linn. (Liliaceae)	Kumaari	Gel from leaves	Anthraquinone glycosides	Purgative, emmenagogue, emollient, Anti - inflammatory
Andrographis paniculata Nees (Acanthaceae)	Kalmegha	Leaves	Diterpenes	Hepatoprotective, antispasmodic, blood purifier, febrifuge
Asparagus racemosus Wild. (Liliaceae)	Shatavaari	Roots	Saponins, sitosterols	Ulcer healing agent, nervine tonic, antigout.
Tinospora cordifolia Miers. (Menispermiaceae)	Amrita, guduuchii	Entire herb	Alkaloidal constituents such as berberine, tinosporic acid	Hypoglycaemic agent, antipyretic.

Terminalia arjuna Roxb. (Combretaceae)	Arjuna	Leaves bark	Flavonoids, oligomeric proanthocyanidins, tannins	Cardiotonic, diuretic, prescribed for Hypertension
Chlorophytum borivilianum Sant. F (Liliaceae)	Safed musli	Roots	Sapogenins	Antifungal.
Abutilon indicum linn. (Malvaceae)	Atibalaa	Whole plant	Flavonoids, triterpenoids	Diuretic, antibacterial
Nyctanthes arbor - tristis L. (Oleaceae)	Paarijaata	Leaf, seeds	Iridoid glucosides	Anti - inflammatory, antispasmodic.
Acacia catechu Willd. (Leguminosae)	Khadira	Leaf	Flavonoids, quercetin	Hypoglycaemic, astringent.
Hibiscus rosa sinensis Linn. (Malvaceae)	Japaa	Flowers	Cyclopropanoids	Antidiarrheal, anti - inflammatory.
Cleome gynandra Linn. (Capperdiceae)	Tilaparni	Leaf, seeds, roots	Hexacosanol, kaempferol	Anti - inflammatory.
Genus Ardisia (Myrsinaceae)	Marlberry	Shrub, Branches and leaves	Peptides, saponins, Isocoumarins, quinones and alkyl phenols	Antimetastatic drug, anti - HIV property.
Bidenspilosa L. (Asteraceae)	Beggar - ticks	Flowers, leaves	Polyacetylenes	Anti - inflammatory, immunosuppressive, antibacterial and antimalarial.
Cannabis sativa (Cannabaceae)	Common hemp	Leaves	Cannabinoids	Immunomodulatory.
Carpobrotus edulis L. (Aizoaceae)	Fig Marigold	Flowers, fruit	Alkaloids	Immunomodulator.
Centellaasiatica Linn. (Umbelliferae),	Brahmi	Herb	Triterpenoid saponins	Immunomodulator.
DracocephalumKotschyi (Lamiaceae)	Dragon - Head	Herb	Essential oil	Immunomodulator.
Echinacea angustifolia (Asteraceae)	Cone flower	Flowers	Polysaccharide	Treatment for common cold, immunomodulator.
Thujaoccidentalis L. (Arborvitae)	White cedar	Leaves	Polysaccharides	Immunomodulator.

Table 2: List of plants having immunomodulatory activity

S. No.	Plant Name	Family	Part Use
1.	*Boerhaaviadiffussa*	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.	*Withania somnifera*	Solanaceae	Whole plant
8.	*Asparagus racemosus*	Asparagaceae	Root
9.	*Panax ginsengs*	Araliaceae	Root
10.	*Azadiracta indica*	Meliaceae	Leaf
11.	*Arnica montena*	Compositae	Dried flowers head
12.	*Echinacea purpurea*	Asteraceae	Flowering top
13.	*Ocimum sanctum*	Lamiaceae	Leaf

***Boerhaaviadiffussa*:**
Boerhaaviadiffusa, (Punarnava; Family Nyctaginaceae), is a reptile weed that is abundant throughout India. In traditional Indian medicine, the roots of this herb are used to treat dyspepsia, jaundice, spleen enlargement, abdominal pain, and antistress agents. Six naik et al. reports the release of boerhaaviadiffussa into hexane, chloroform & ethanol solvents, separating two different compounds namely Bd - I (eupalitin - 3 - O - h - Dgalactopyranoside) and Bd - II (eupalitin) by Flash chromatography. Hexane extraction significantly inhibited PHA - induced proliferation of human peripheral mononuclear cells at concentrations of 10 µg / ml, while chloroform and ethanol extract provided this activity at concentrations of 50 µg / ml. The pressure of Bd - I and Bd - II depends on the dose and ranges from 63 - 98% to 500 µg / ml to 7 - 14% to 5 µg / ml.

On the other hands the effect of chloroform release on NK cell is 84%, ethanolic extract is 48%but Bd - I & Bd - II are much lower i. e.3% and 12% respectively. [42]

***Curcuma longa*:**
Curcumin is an active component of curcuma longa linn family Zingiberaceae India is the largest producer of curcuma longa linn (about 90 percent). the perfect product of the world). Curcuma is a genus about 70 species in rhizomatous herbs is distributed in southeast Asia especially India, China, Thailand and Malaysia. Curcumin is used to treat anti - inflammatory, antiarthritic, common cold & cough, jaundice agent. *Gaoa et al*. extracted curcumin from the curcuma longa plant. They have reported that the effect of curcumin on mitogen / antigen has led to an increase in splenic lymphocytes, the secretion of cytotoxic T - lymphocytes (CTLs), lymphokine activated killer cells (LAK) and the production of cytokines by T - lymphocytes and - macrophages. They examined the effect of curcumin on the proliferation of splenic lymphocytes with a 3H - thymidine uptake assay. Curcumin also inhibits IL - 2 - induced proliferation of splenic cells. IL - 2 inhibition cell proliferation was dependent on volume; as the increase in the effect of pressure was curcumin rises from 6.25 to 25 mmol / L. IL - 2 is activated stem cell proliferation was completely inhibited by curcumin at 25 mmol / L. [43]

***Rhododendron spiciferum*:**
Rhododendron spiciferum plant of the family Ericaceae. They will be widely used as a medicinal plant because the proanthocyanidin A - 1 (PAA - 1) of the active ingredient is widely used in health care. Proanthocyanidin A - 1 (PPA - 1) is used as a free radical scavengers, anti - bacterial agents and active enzyme inhibitors. They also exhibit the activity of vasodilators, anti - allergic, anti - inflammatory, cardio - protective, immune - stimulating, antiviral and estrogenic activities. *Y. Z. Liu et al.*, Extracted from rhododendron extracted 70% acetone, Water, petroleum ether, Ethyl

acetate, n - Butanol respectively. They also differentiate proanthocyanidins A - 1 from the chromatography extract using Chloroform: Acetone (1: 0 → 6: 4) as an opportunity to produce five fractions based on silica gel thin layer chromatography (TLC). One - fifth of these extracts were reconstituted for chromatographic using the solvent Chloroform: Methanol (100: 0 → 40: 60) and proanthocyanidin A - 1 isolate. 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. [44]

Caesalpinia bonducella

Caesalpinia bonducella of the Caesalpiniaceae family. It is best known as Nata Karanja. It is a traditional Indian plant but also found in Myanmar, Sri Lanka. ICaesalpinia prickly shrub, a globe - shaped seed with a smooth, shiny surface. The seeds of these plants contain a thick, fragile shell with a yellowish - white oil. Caesalpini Bonducella is used for herbal remedies such as antipyretic, antidiuretic, anthelmintic and antibacterial, anti - anaphylactic and antidiarrheal, antiviral, antiasthmatic, antiamoebic and anti - estrogenic. In the treatment of liver and tumor disorders, Caesalpiniathey have been used traditionally. [45]

Tinospora cordifolia

Tinospora cordifolia of the family Menispermaceae. This is a never - ending stream spread across the tropical Indian subcontinent. It is classified as Ayurveda and is best known for its adaptogenic and immunomodulatory activity in the fight against infection. The activity of this drug appears to be due to the alkaloid. The drug exhibits immunomodulatory activity. It is shown to be effective against various types of test infections. [46]P. K. Raveendran Nair et al was independent of the Tinospora cordifolia extract known asa - d - glucan RR1. The thermal extraction process used for extraction. In the methanol extraction process, Trichloroacetic acid is used as a solvent. RRA - 1 compound is separated from this extract in the form of column chromatography and lyophilization procedure. They have reported the effect of tinospora cordifolia extract on lymphocytic activation. The extraction dose of 100 µg / ml will give the effect of lymphocytic activation i. e. performance of 39%, - cells, 105% T - cells and 331% NK cells respectively. In this case the effect ofrelease from NK cells is high, this is an important factor because NK cells are important influencing the immune system. RR1 created a combination of IL - 1h (1080 pg), IL - 6 (21, 833 pg), IL - 12 p40 (918.23 pg), IL - 12p70 (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 cause the production of IL - 2, IL - 4, IL - 10, TNF - h and IFN - a. [47].

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. 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 are 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. [48]

Nelumbo nucifera

Nelumbo nucifera is a plant of the genus Nymphaeaceae. This plant is a well - known aquatic plant used as a traditional medicine in India. Extracts of the rhizome of Nelumbo nucifera, using hypoglycaemic, antidiarrhoeal, antimicrobial, diuretic, antipyretic, psychopharmacological, anti - inflammatory activity. The seeds of this plant are used for the following activities which include anti - ischemic, antioxidant, hepatoprotective, Antiproliferative, anti - inflammatory. This plant contains betulinic acid and a steroidal pentacyclic triterpenoid. each extract of this plant is used for immunomodulatory activity. *D. Mukherjee et al.* reported immunomodulatory effect of extract plant (Nelumbonucifera), Swiss albino mice. The extraction (NNSE and NNRE) of the rhizome and seeds was extracted 70% ethanol by cold maceration process. Work has been reported dose dependence i. e. NBT enhancement (testing to reduce Nitro blue tetrazolium) reduction most noted for your high doses of both extracts, 300 mg / kg (NNSE, $P < 0.001$; NNRE, $P < 0.01$) and have a lower dose of 100 mg / kg compared to controls100 mg / kg ($P < 0.01$), 300 mg / kg ($P < 0.001$). During their study they noticed that the adhesion of neutrophils to the nylon fiber was increased in both NNRE and NNSE - controlled groups compared to controls and concluded that hydro alcoholic extracts of the rhizome and Nelumbo nucifera seeds showed stimulation immune system by changing immunological parameters and suggesting possible treatments benefits of plant components in immunomodulation. [49]

Allium sativum

Allium sativum is an important medicinal plant with immunomodulatory effects. Three immunomodulatory proteins are separated from the stem by Q - Sepharose chromatography of 30 kD ultrafiltrate garlic extract. All of these proteins show mitogenic activity in human blood lymphocytes, murine splenocytes and thymocytes. P. Venkatesh et al., Isolated these proteins from raw garlic, and examined their effects on the immune system (lymphocytes, mast cells and basophils) with respect to mitogenicity and high sensitivity. The extraction of garlic was prepared by mixing the bulbs in phosphate buffer saline (ph, 7.4). Followed by rain of ammonium sulphate and separated by ultrafiltration, as well as anionswitch chromatography using Q - Sepharose (High Performance) column unbuffered 20mM 1, 3 - diaminopropane taken in a ratio of 1: 10 (w / v), Tris – HCl buffer, pH 8 and NaCl. The eluted fractions monitored by suction at 280 nm. ImPs of rich garlic, QR - 1

and QR - 2, identified in current research as lectins oragglutinins ASA II and ASA I, have been found to have potent mitogenic activity with possible usabilityin therapeutic immunomodulation. [50, 51]

2. Conclusion

Immunomodulatory drugs are agents that can change the body's immune system, either by increasing the immune response called immunostimulants or by slowing down the immune response called immunosuppressants. These drugs are widely used in autoimmune diseases, allergies, AIDS, cancer and other viral infections. Modern health care in developing countries like India remains a far - reaching goal due to the economic crisis. Only a few plants have been tested for immunomodulatory functions. From the above review, it is clear that there are a few medicinal plants and marine products that have an immune function but sufficient evidence does not permit their use in clinical practice. Immunomodulatory agents will therefore find additional value in future research of herbal medicines.

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