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Immunomodulatory Mechanistic Potentials of Herbals

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Abstract

In the medicinal system of Ayurveda, several plants have been used for the treatment of various illnesses due to their biological effects exerted by specific constituents present in them. It incorporates holistic approaches for the diagnosis, treatment, and prevention. Also referred to as natural or traditional medicines, herbal medicine has endured through various cultures and civilizations. Due to various lifestyle changes and environmental factors, there is a deteriorating effect on the immunity of individuals. Remedy for several issues can be found in nature, which has proven to be of lesser side effects as well as cost-effective. Immunomodulators are one of the therapeutically used categories of plants or their based drugs that are capable of inducing, stimulating, or suppressing any immune system component, which can affect both innate and adaptive immune responses. The objective of this paper is to highlight various Ayurvedic or herbal plants and their immunomodulatory constituents. Ongoing clinical trials on a few of the herbal plants have also been included. Moreover, the mode of action and plant origin, including other uses of numerous prominent plant-based lead compounds, has also been extensively discussed.

INTRODUCTION

For ages, medicinal plants are used for the treatment of various illnesses and ailments. These plants are therapeutic due to the chemicals they possess and bring about outcomes similar to conventional drugs. Moreover, to eliminate the undesired effects of harmful or toxic substances, which may or may not be present in these plants, the crude products are processed well. According to the World Health Organization (WHO), about three-quarters of the world population relies upon traditional remedies (mainly herbs) for the health care of its people [1].

India's traditional medicinal system, Ayurveda, originated over six thousand years ago and is the science that deals with physical well-being and approaches to cure diseases. "Ayu" connotes life, and "Veda" means knowledge. It accentuates the significance of a healthy lifestyle and diet along with drugs (majorly consisting of plants) as the therapy. The concept "Vyadhirodhak Chamatav" describes the competence of our bodies to resist diseases, and this is incorporated into Ayurvedic therapeutics, wherein the prevention of diseases is the focus rather than its cure [2]. Among the ancient Indian scriptures, the Vedic literature extensively provides a reference to various plants and their uses in the prevention and treatment of diseases. The other Vedic literature and the number of plants being referred to are as follows [3]:

Rama and Sama Veda- 67 plants
Yajour Veda- 81 plants
Atharva Veda- 289 plants
Brahamana- 129 plants
Upanishads-31 plants

Recently, research has shown that immunomodulation can be a replacement for conventional chemotherapy. This is particularly advantageous when the host's defense mechanism must be activated in impaired immune responsiveness or autoimmune disorders and organ transplantation. However, it is not until recent times that the use of chemicals for modulating immunity has gained importance. However, original Ayurvedic texts like Charaka and Sushruta Samhita are written in Sanskrit. Therefore, the translation and interpretation of terms denoting "immunomodulator" or "immunostimulant" have been the primary source of research material for several scientists. At present, researchers are focusing more on ayurvedic plants as immunomodulators as allopathic drugs pose more side effects in comparison to these plants. The constituents present, whether alkaloids, flavonoids, terpenoids, polysaccharides, lactones, or glycoside products, exert effects that cause alterations in the immunomodulatory properties [2].

The host's immune system plays a pivotal role in the upkeep of immunological functions, internal environment, and physiological functions. The immune system has to distinguish between its cells and invader pathogens. Consequently, it performs other integrated functions like detecting the microbes, initiation of inflammation, clearance of microbes, cell damage or death, and wound healing.

The host immune system is also a defense system that impedes pathogen entry and interaction of immune cells with these pathogens into the microbial tissue to regulate balance [4]. It comprises many co-dependent cells that mutually defend from bacterial, viral, fungal, parasitic, and tumor cell growth. Engulfing bacterial cells, eliminating parasites, viral cells, or tumor cells are how the immune cells respond to any emergency. These immune cells rely on the T-helper subset for activation signals in the form of secretions called cytokines, lymphokines, or more [3].

The basic architecture of the immune system is multi-layered, with defenses on several degrees. If the pathogen enters the body, it is fought by the innate, acquired, or adaptive immune system. Thus, the immune system can be classified based on function as the innate immune system (non-specific immune system) and adaptive immune system (specific or acquired immune system). Each system comprises a whole host of cells and molecules that act together in intricate ways to identify and purge the body of any existing pathogens. This identification and purging depend on chemical bonding: surfaces of immune system cells are covered with various receptors, some of which chemically bind to pathogens.

In contrast, others bind to other immune system cells or molecules to enable the complex signaling system that mediates the immune response. The first barrier against any invading contagion is the skin. Physical, microbiological, and chemical barriers are all comprised of innate immunity. Nevertheless, cytokines, acute phase proteins, macrophages, monocytes, complement, and neutrophils are the major mediators of the immune system that furnish prompt protection. Via a gene rearrangement process, pathogen (antigen)-specific B and T lymphocytes are produced in adaptive immunity. The body's exposure to the antigen to produce an adaptive immune reaction that develops in weeks/months but may last through whole life is called active immunity [1].

Over the last three decades, there has been unprecedented interest in the immune system as a potential target of toxicity following exposure to drugs, chemicals, or environmental pollutants, collectively referred to as xenobiotics. Since cells of the immune system undergo continual proliferation and differentiation for self-renewal to maintain immune-competence is also often affected by xenobiotics resulting in a cellular imbalance. In addition, the interaction of xenobiotics with the immune system may result in toxic immune alterations in host defense mechanisms against pathogens or neoplasia or dysregulations of the immune response, causing allergy, hypersensitivity, and autoimmune reactions.

Immunodeficiency: Immunodeficiency occurs when one or more of the components of the immune system are inactive. Immunodeficiency can be inherited or "acquired." Chronic granulomatous disease, where phagocytes have a reduced ability to destroy pathogens, is an example of an inherited or congenital immunodeficiency. In addition, infectious diseases acquired immune deficiency syndrome (AIDS) and some types of cancer result from acquired immunodeficiency.

Autoimmunity: Overactive immune responses comprise the other end of immune dysfunction, particularly autoimmune disorders. Here, the immune system fails to distinguish between self and non-self adequately and attacks part of the body. Under normal circumstances, many T-cells and antibodies react with "self" peptides. One of the functions of specialized cells (located in the thymus and bone marrow) is to present young lymphocytes with self-antigens produced throughout the body and to eliminate those cells that recognize self-antigens, preventing autoimmunity.

Hypersensitivity: Hypersensitivity is an immune response that damages the body's tissues. They are divided into four classes (Type I-IV) based on the mechanisms involved and the time course of the hypersensitive reaction [5]. Three types of hypersensitivity are antibody-mediated (types I-III), while the fourth is cell-mediated (type IV). Hypersensitivity occurs in two phases: the sensitization phase and the effectors' phase. Sensitization occurs upon initial encounter with an antigen; the effector's phase involves immunologic memory and results in tissue pathology upon a subsequent encounter with that antigen [3].

Immunomodulators deal with the natural and artificial agents that can stimulate or depress any immune system component, including innate and adaptive immunity. Clinically, immunomodulators can be classified into the following three categories:

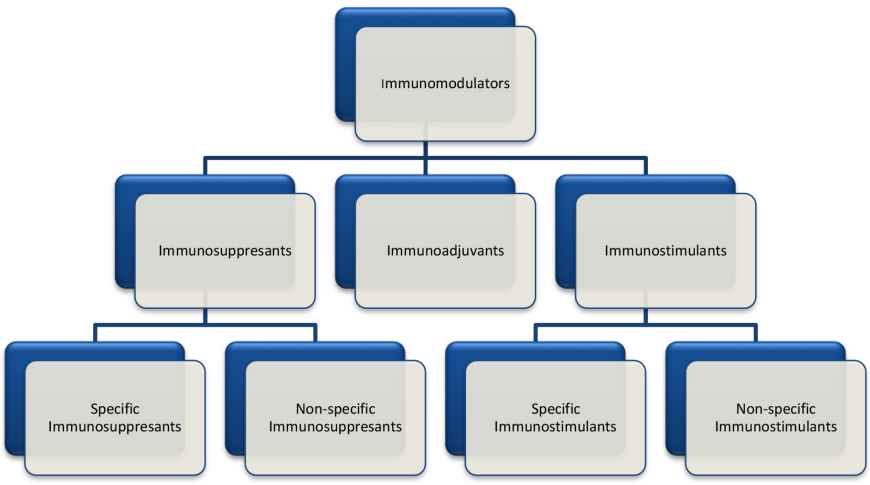

Figure 1: Immunomodulator Classification

Immunoadjuvants

These are specific immunomodulators used to improve the efficacy of the vaccine. They can be utilized as selectors between cellular and humoral (helper T1 and T2) cells, immunoprotective, immunodestructive, and reagenic (IgE) versus IgG type immune responses.

Immunostimulants

These are substances that activate the components of the immune system and enhance the body's resistance to infection. Immunostimulants improve the resistance against autoimmunity, cancer, allergy, and infection. Some of the immunostimulant drugs are-
Synthetic compounds- e.g. Isonosine, Levamisole.
Immune globulin
Cytokines- e.g. interferon (INF-α), Interleukins (IL-2)
Peptides- e.g. dialyzable leukocyte extracts, neuropeptides, thymic factors.
Microorganisms

Immunosuppressant

These are given as a combination regimen that suppresses the immune system. They are used before organ transplantation and infection-associated immunopathology, hypersensitivity reactions, and autoimmune diseases. Some of the immunosuppressants are-
Specific T- cell inhibitors (calcineurin inhibitors)- E.g. Cyclosporine, Tacrolimus
Cytotoxic drugs (Antiproliferative drugs) - E.g. Azathioprine, Cyclophosphamide, Methotrexate, Chlorambucil, Mycophenolate mofetil.
Glucocorticoids- E.g. Prednisolone and others.
Antibodies- E.g. Muromonal CD3, Antithymocyteglobulin, Rho (D) immunoglobulin (69)

Existing synthetic Immunomodulators merits and demerits

There is an eclectic assortment of synthetic, natural, and recombinant compounds are accessible in the market like Isonosine, Levamisole, interferon (INF-α), Interleukins (IL-2) cyclosporine, tacrolimus, Muromonal CD3, anti-thymocyte globulin, Rho (D) immunoglobulin, and some others are significantly used. For example, microbial immunomodulators, Bacille Calmette-Guérin (BCG), have used Urothelial carcinoma and infectious diseases for non-specific immunity. The invention of cytokines has led to the assessment of the efficacy of various interleukins and IFN in the immunotherapy of cancer. Cytokines are molecular messengers that allow the cells of the immune system to communicate with one another. While these synthetic immunomodulating drugs have numerous benefits, their adverse side effect profile and generalized effect throughout the immune system pose a significant limitation to the general deliberate use of these drugs and warrants the search for more effective and safer agents exerting immunomodulatory activity. So, researchers focus more on ayurvedic medications to eliminate the adverse side effects of synthetic drugs and find more effective therapeutic outcomes [6].

METHOD

This review was carried out by searching extensively electronic databases like Google Scholar, PubMed, Scopus, JSTOR, and Clinical Trials Registry India. No time limit for data publication, language, or geographical location was set. The criteria set for considering the review was if the study had reliable and adequate material on assessing the Immunomodulatory effects of the plants. Studies with no ample information or abstracts were excluded. In-vivo and in-vitro studies were included if the criteria were met. The primary authors were not contacted but only the information published was included in the review.
Initial screening was done based on titles and abstracts. Further on, full studies were retrieved and inspected for eligibility. The chosen articles were taken using search terms like "ayurvedic plants", "Immunomodulatory herbs", "Indian herbs", "ayurvedic herbs with immunoconstituents", "immunostimulant plants", "immunosuppressant herbs" and "mechanism of Immunomodulatory plants".
Data that was collected from the 54 eligible papers were extracted into a custom-made tabular form that included all necessary information in fields for common name, the Immunomodulatory constituents, mechanism of action, and other known uses of the herbs. Tables 1 and 2 demonstrate the studies included in the review.

Table 1: Plants with immunomodulatory actions, major constituents, and other uses

S. No	Scientific name	Common name	Phytoconstituents	Mechanism of action	Other uses	References
1	*Withania somnifera* (Solanaceae)	Ashwagandha	Steroid saponin (sitoindoside IX, X), steroidal lactone (withanolide-5, 20α,(R)-dihydroxy-6α,7αepoxy-1-oxo-5α-witha-2,24-dienolide, 3-β-hydroxy-2,3-dihydro-withanolide)	An increase in total WBC, antibody-forming cells, and bone marrow cells significantly	Sedative, diuretic, anti-inflammatory, anti-stress agent, adaptogen	[7]
2	*Acacia catechu* (Fabaceae)	Khair	Flavonoids, quercetin	Increase in the serum immunoglobulin levels, macrophage induced phagocytosis	Antidiarrheal, antiseptic, anthelmintic, dessicative, blood purifier, and astringent.	[8]
3	*Jatropha curcas* (Euphorbiaceae)	Physic nut, Barbados nut	Flavonoid glycosides(apigenin 7-O-β-D galactoside, orientin, vitexin, vicenin II)	Increase in cellular and macrophage activity	Antimicrobial, anti-cancer, and anti-HIV activity	[9]
4	*Morus alba Linn* (Moraceae)	Mulberry	Flavonoids, anthocyanins	Increased lymphocyte proliferation, increased Delayed-Type Hypersensitivity (DTH) response, and decreased antibody production from B cells	Treatment of dizziness, insomnia, premature aging, and DM2.Protective effect against atherosclerosis, liver and kidney disorders, and inflammation	[10]

5	*Achilleawilhelmsii* (Asteraceae)	Yarrows	Flavonoids, alkaloids, polyacetylenes, coumarins, triterpenes	The stimulatory effect on both humoral and innate immunity. Humoral response activated by macrophages and B- lymphocytes setup involved in the antibody production.	Treatment of wounds, bleedings, headache, inflammation, pains, spasmodic diseases, flatulence, and dyspepsia	[11]
6	*Sophorasubprosrate* (Fabaceae)	Kowhai	Polysaccharides	Stimulated proliferation and IFN-γ secretion of murine splenic lymphocytes, increased the levels of interleukin-6 and tumor necrosis factor-α, spleen index, glutathione level, glutathione peroxidase activity, and lysozyme activity in the immunosuppressed mice	Antioxidant, anti-cancer, anti-asthmatic, anti-neoplastic, antimicrobial, antiviral, antidote, antipyretic, cardiotonic, anti-inflammatory, diuretic and in the treatment of skin diseases like eczema, colpitis, and psoriasis	[12]
7	*Picrorhizascrophulariiflora* (Plantaginaceae)	Pennell	Iridoid glycosides (III, V, 6-feruloyl-catalpol, and minecoside, amphicoside, scrocaffeside A)	Inhibiting the classical pathway of complement, the release of reactive oxygen species by activated neutrophil leukocytes, and the mitogen-induced proliferation of T lymphocytes	Treatment of jaundice, acute viral hepatitis, fever, allergy, asthma, eczema, and vitiligo	[13]
8	*Picrorhiza kurroro* (Plantaginaceae)	Kutki	Iridoid glycoside (kutkin)	Increases in the proliferation of lymphocytes, cytokine levels (IL-4 and IFN-γ) in serum.	Treat disorders of the liver and upper respiratory tract, reduce fevers, and treat dyspepsia, chronic diarrhea, and scorpion sting	[14]
9	*Plantago Asiatica* (Plantaginaceae)	Chinese plantain	Polysaccharides (Ara and Xyl)	Expressed higher levels of MHC class II molecules and major co-stimulatory molecules such as CD80 and CD86, CCR7 mRNA expression	Treat the liver disease, stomach problems, and urinary system inflammation	[14]
10	*Caesalpiniabonducella* (Fabaceae)	NataKaranja	Flavonoids, phenolic acids	Increase the total WBC count, potentiate non-specific immune response, improve humoral as well as cell-mediated immunity effectively	Anthelmintic, febrifugal, periodic, tonic, and vesicant. They are used to treat colic, convulsions, leprosy, and palsy	[15]
11	*Allium sativa* (Amaryllidaceae)	Garlic	Amino acid (alliin), volatile oil{ garlic oil(s ajoene [(Z,E)-4,5,9-trithiadodeca-1,6,11-triene-9-oxide], Z,E-devinylajoene, vinyldithiin, and some thiosulfinate)}	Inhibiting Th1 pro-inflammatory cytokines, inhibitory effect on NF-κB activation, reducing pro-inflammatory cytokine-like IL-1β and TNF-α, without changing IL-10 level human whole blood	Treat several ailments, including fevers, diabetes, rheumatism, intestinal worms, colic, flatulence, dysentery, liver disorders, tuberculosis, facial paralysis, high blood pressure, and bronchitis	[16]
12	*Panax ginseng* (Araliaceae)	Ginseng	Polysaccharides	Activation of B and T cell proliferation and increased cytotoxic activity increased macrophage production of reactive nitrogen, activated spleen cells	Adaptogen, for anxiety, athletic/physical stamina enhancement, cognitive function, enhancement, depression, fertility (male), headaches, immunostimulant, menopausal hot flashes, and impotence.	[17]
13	*Cynodon dactylon* (Poaceae)	Bermuda grass	Phenolics	Enhanced the humoral antibody response to the antigen and significantly potentiated the cellular immunity	Anti-cancer, convulsions, cough, cramps, diarrhea, dropsy, dysentery, epilepsy, headache, hemorrhage, hypertension, hysteria, measles, rubella, snakebite, sores, stones, tumors, urogenital disorders, warts, and wounds	[18]
14	*Pteridiumaquilinum* (Dennstaedtiaceae)	Bracken or Eagle fern	Flavanoid (quercetin)	Reduced DTH response, IFNγ production by NK cells during Th1 priming	Anti-emetic, antiseptic, appetizer and tonic, treatment of rheumatism	[19]
15	*Terminalia arjuna* (Combretaceae)	Arjuna	Flavonoids, oligomeric proanthocyanidins, tannins	Increased secondary immune response, increased IL-2 and interferon-gamma levels	Asthma, bile duct disorders, scorpion stings, and poisonings	[20]
16	*Rhus Toxicodendron* (Anacardiaceae)	Poison ivy	Catechol (urushiol)	Stimulates antibody production, increased chemotaxis, a potent stimulatory effect on intracellular oxidative processes	Skin irritations, rheumatic pains, mucous membrane afflictions, and typhoid type fever	[21]
17	*Actinidiaerinthia Benth* (Actinidiaceae)	Kiwifruit	Polysaccharides (AEPA, AEPB, AEPC, AEPD)	Promotessplenocytes proliferation, NK cell and cytotoxic T-lymphocytes activity, IL-2 and IFN-γ production from splenocytes, and serum antigen-specific antibody levels	Antitumor, anticoagulant, and anti-inflammatory properties	[22]
18	*Boerhaaviadiffusa* (Nyctaginaceae)	Punarnava	Alkaloid	Enhancement in the number of plaque-forming cells, enhanced proliferation of splenocytes, thymocytes, and bone marrow cells, reduced TNF-α, IL-1β, and IL-6.	Intestinal colic, kidney disorders, cough, hemorrhoids, skin diseases, alcoholism, insomnia, eye diseases, asthma, and jaundice	[23]
19	*Andographispaniculata* (Acanthaceae)	Green chiretta	Diterpenes, andrographolide	Modulate the innate and adaptive immune responses by regulating macrophage phenotypic polarization and antigen-specific antibody production. Regulating macrophage activation and polarization	Anti-inflammation, antitumor, antidiabetic and cardioprotective activities	[24]

20	*Dioscorea japonica* (Dioscoreaceae)	Yam	Alkaloid (dioscorin), vanillic acid, gallic acid, p-coumaric acid, palmitic acid, linoleoic acid, squalene	Significant enhancement of phagocytosis and natural killer cell cytotoxic activity, IgA increased, lymphoid cells proliferation.	Allergen, antihypertensive, antioxidant, lectin activities and the protecting role on airway epithelial cells	[25]
21	*Curcumin longa* (Zingiberaceae)	Turmeric	Polyphenols (curcumin, curcuminoids, demethoxycurcumin)	Modulates the function of T cells, B cells, dendritic cells, monocytes, macrophages, and neutrophils.	Antitumor, anti-inflammatory actions, anti-bacterial, antioxidant, blood sugar lowering, antiproliferative and wound-healing properties	[26]
22	*Tinospora cordifolia* (Menispermaceae)	Heart-leaved moonseed	11-hydroxymustakone, N-methyl-2-pyrrolidone, N-formyl annonain, cordifolioside A, magnoflorine , tinocordiside, syringing, α-D-glucan	Increased the phagocytic function of human neutrophils, Innate immune activation also triggers and paves the way for adaptive immune response by antigen-specific T and B lymphocytes.	General tonic, anti-inflammatory, anti-arthritic, antimalarial, aphrodisiac, anti-allergic antidiabetic, antihepatotoxic and antipyretic	[27]
23	*Abrus precatorius* (Fabaceae)	Rosary pea	Lectin (agglutinin)	Increases the expression of activation markers (CD25, CD71) in B and T cells, induces the production of cytokines like IL-2, IFN-γ, and TNF-α, and stimulates the innate effector arms, like macrophages, by up-regulating pro-inflammatory cytokine expression. Increased production of nitric oxide and hydrogen peroxide and a high phagocytic and bactericidal activity of macrophages	Anti-inflammatory, antiallergic, and anti-cancer properties	[28]
24	*Aristolochialonga* (Aristolochiaceae)	Barraztam	Alkaloid (aristolochic acid)	Significant activity and increased phagocytic response, both cellular and humoral antibody response	Abdominal pain and infections of the upper respiratory tract, antidote, anti-cancer	[29]
25	*Berberis aristata* (Berberidaceae)	Indian barberry	Alkaloids (berberine, berbamine)	Significant reduction in serum inflammatory cytokine levels. Protein expression of pro-inflammatory markers, IL-1β, IL-6, TNF-R1, and COX-2, was found to be reduced in stimulated macrophages, whereas anti-inflammatory cytokine, IL-10, was up-regulated in peritoneal macrophages.	Anti-bacterial, antiperiodic, antidiarrheal, and anti-cancer, and it is also used in the treatment of ophthalmic infection	[30]
26	*Clitoriaternatea* (Fabaceae)	Asian pigeon-wings	Flavonoid and phenolic compounds	Increased levels of reactive oxygen species, which may cause premature immunosenescence, enhance total white blood cells, red blood cells, T-lymphocytes, and B-lymphocytes	Cooling, laxative, diuretic, anthelmintic, they are useful in severe bronchitis, asthma and hectic fever, nootropic, anxiolytic, antidepressant, anticonvulsant, sedative, antipyretic, anti-inflammatory, analgesic activities, enhances the memory, and increases acetylcholine content and acetylcholinesterase activity in rats	[31]
27	*Cymbopogon martini* (Poaceae)	Palmarosa	Monoterpenoid(geraniol)	Increased IL-10 production by human monocytes.	Antimicrobial, anti-fungal, antiviral, anthelmintic, antioxidant, and cytotoxic properties	[32]
28	*Allium stipitatum* (Amaryllidaceae)	Persian shallot	Allin, allicin, and organosulfur compound (allylsulfides)	Modulating cytokine secretion, phagocytosis and cell activation, activation of humoral immune response and synthesis of Ig, mitogenic stimulator.	Anti-bacterial, cardioprotective, anti-cancer, anti-inflammatory, antioxidant.	[33, 34]
29	*Aloe vera* (Asphodelaceae)	Aloe	Anthraquinone glycosides, polysaccharides (acemannan, glucomannan, acetylated mannan, galactogalacturan)	Stimulate leukocyte and lymphocyte and release of IL-1, IL-6, and TNF-α. Modulate immune response by augmenting secondary humoral immunity. It also stimulates cytokines which cause activate lymphocytes	Anti-inflammatory, anti-arthritic activity, anti-bacterial, hypoglycemic effects, and useful effects in skincare like skin repair, skin hydration, anti-aging, wound healing, and many more.	[34, 35]
30	*Asparagus racemosus* (Asparagaceae)	Shatavari	Glycosides (saponins), sterols (sitosterols)	Enhance immunoglobulin production and stimulate macrophages and activate T-cells and NK cells, where NK cells stimulate the lymphocytes and other immune cells like macrophages and B cells. Enhanced phagocytic activity of the macrophages and polymorphs	Galactagogue effect, antitussive effect, adaptogenic, ant secretory and antiulcer, antibacterial, antiprotozoal, antihepatotoxic, anti-neoplastic, antidiarrheal, antiurolithiatic activity	[34, 36]
31	*Azadirachtaindica* (Meliaceae)	Neem	Phenolic acid (gallicacid), flavonol (epicatechin, catechin)	Boosts both the lymphocytic and cell-mediated systems, including "Killer T" cells. Enhance phagocytic activity and MHC class-II expression indicating enhancement of their antigen-presenting ability, enhance lymphocyte proliferation	Anti-inflammatory, anti-arthritic, hypoglycaemic, antipyretic,diuretic, anti-gastric ulcer, anti-fungal, anti-bacterial, spermicidal, anti-malarial, anti-tumor, hepatoprotective, anti-oxidant	[37]

32	*Ocimum sanctum* (Lamiaceae)	Tulsi	Monoterpenoid(carvacrol), glycoside (apigenin), triterpenoid(ursolic acid)	Immunomodulatory effect show by increase in IFN-Y, IL-4, helper cells, NK cells, increasing neutrophils and lymphocyte and enhancing phagocytic activity and phagocytic index	Antifertility, anti-cancer, ant diabetic, anti-fungal, antimicrobial, hepatoprotective, cardioprotective, anti-emetic, antispasmodic, analgesic, treatment of bronchitis.	[34, 38]
33	*Phyllanthusemblica* (Phyllanthaceae)	Indian gooseberry	Tannin (corilagin, geraniin,chebulagic acid), phenolic acid (gallic acid, ellagic acid), flavonol (quercetin),	Stimulation of splenocyte proliferation and shows cytotoxic effects in in-vivo studies	Analgesic, anti-inflammatory, antipyretic, anticonvulsant, spasmolytic, antidiarrhoeal, antisecretory, bronchodilatory, urinary bladder relaxant	[34, 39]
34	*Hibiscus rosasinensis* (Malvaceae)	Shoeblack plant	Cyclopropanoids	Potentiate the phagocytosis, cell-mediated, and humoral antibody-mediated activation of T and B cells.	Antioxidant, antimicrobial, antidiabetic, antiulcer, hepatoprotective, antifertility, and anti-inflammatory properties	[40]
35	*Cleome gynandra* (Cleomaceae)	Shona cabbage	Flavonol (kaempferol)	Increase phagocytosis is influenced by the activation of macrophages; the activated macrophages secrete several cytokines, which in turn stimulate other immune cells.	Anti-inflammatory activity, free radical scavenging activities, anti-cancer activity, antidiabetic.	[41]
36	*Cissampelospareira* (Menispermaceae)	Velvetleaf	Alkaloids (hyaline)	Increasing total WBC count, reduction in antibody production	Treatment of ulcer, wound, rheumatism, fever, asthma, cholera, diarrhea, inflammation, snakebite, malaria, rabies	[42]
37	*Bauhinia variegata* (Fabaceae)	Orchid tree	Flavonoids and sterols (beta-sitosterol, lupeol)	Significant increase in neutrophil chemotactic movement, increased phagocytic activity	Anti-bacterial, anti-fungal, anti-malarial, pain-reducing, swelling-reducing, cytotoxic, fever-reducing, and thyroid hormone regulating properties.	[43]
38	*Ficus carica* (Moraceae)	Common fig	Phenolic acids, flavonoids, polyphenols (coumarins), sterols	Enhanced the production of IL-4, IL-6, TNF-α, and IFN-γ	Treatment of anemia, cancer, diabetes, leprosy, liver diseases, paralysis, skin diseases, and ulcers	[44]
39	*Capparis zeylanica* (Capparaceae)	Ceylon caper	. Flavonoids	Stimulates both cellular and humoral immune responses by significantly ameliorated the total WBCs count, RBCs count, hemoglobin, and platelets count and also restored the myelosuppressive effects induced by cyclophosphamide	Anti-emetic, increasing appetite	[45]
40	Trapa bispinosa (Trapaceae)	Water chestnut	Flavonoids, proteins, and carbohydrates	Influenced T-cell production, enhanced neutrophil count, phagocytosis by cells, and humoral response	Bitter, astringent, stomachic, diuretic, febrifuge, and antiseptic	[46]
41	*Chlorophytum borivilianum* (Asparagaceae)	Musli	Triterpene(sapogenins)	Up-regulation of macrophages, dendritic cells, and B-lymphocyte subsets involved in antibody synthesis	Aphrodisiac agent, revitalizer, remedy for diabetes, arthritis and increasing body immunity, curative for natal and postnatal problems, for rheumatism and joint pains, increase lactation in feeding mothers, also used in diarrhea, dysentery	[47]nic-resource-num></record></Cite></EndNote>
42	*Thuja occidentalis* (Cupressaceae)	Northern white cedar	Polysaccharides	Enhanced the NK cell activity, decreased the serum elevated level of pro-inflammatory cytokines such as IL-1β, IL-6, GM-CSF, and TNF-α, elevated serum levels of IL-2 and tissue inhibitor matrix metalloproteinases	Treatment of respiratory tract infections such as bronchitis, bacterial skin infections, and cold sores. It is also used for painful conditions, including osteoarthritis trigeminal neuralgia	[48]
43	*Viscum album* (Santalaceae)	Mistletoe	Viscotoxins and mistletoe lectins	Induces the secretion of various cytokines like IL-1, IL-2, IL-5, IL-6, IFN-γ, IFN-α, and GM-CSF and serum levels of IL-12 and the in vitro production of IL-2 and INF-γ, activation of NK cells	Treatment of issues such as hypertension, diplopia, severe cold, frequent vertigo, asthmatic conditions.	[49]
44	*Salicornia herbacea* (Amaranthaceae)	Glasswort	Polysaccharides	Production of TNF-α and IL-1β, NO	Treating inflammation, diabetes, asthma, hepatitis, cancer, gastroenteritis	[50]
45	*Silybum marianum* (Asteraceae)	Milk Thistle	Flavonolignan(silymarin)	Increase in acid phosphatase activity, lysozyme and nitric oxide content, macrophage phagocytosis	Treatment of liver and biliary disorders	[51]
46	Rhodio laimbricata (Crassulaceae)	Himalayan stonecrop	Phenolics	Induction of TNF-α production, TLR-4 activation,	Antioxidant, anti-aging, radioprotective	[52]
47	*Moringa oleifera* (Moringaceae)	Drumstick Tree	Vitamin A, B, C, tetraterpenoids(carotenoids), glycosides (saponins)	Increment in WBC, lymphocyte, neutrophil counts, and neutrophil adhesion	Antioxidant, aphrodisiac, prevents pregnancy, boosts the immune system, and increases breast milk production.	[53]
48	*Mollugo verticillata* (Molluginaceae)	Green carpetweed	Flavanoids (quercetin), glycosides (triterpenoid glycosides)	Increase in NO production, increased cytokine production, increased TNF-α activity	Anti-fungal and anti-inflammatory properties	[54]

49	*Matricaria chamomilla* (Asteraceae)	German chamomile	Polyphenols	Blocks signal transduction pathways like Mitogen-Activated Protein Kinases (MAPK)	Treatment of cough and bronchitis, fevers, colds, inflammation, infection, wounds, and burns	[55]
50	*Lycium barbarum* (Solanaceae)	Matrimony Vine	Polysaccharides	Increase in lymphocytes, IL-2, and IgG levels	Anti-aging agent, treatment of blurry vision, abdominal pain, infertility, dry cough, fatigue, dizziness, and headache	[56]
51	*Larrea divaricate* (Zygophyllaceae)	Chaparral	Lignans	The rapid increase in ROS and loss of mitochondrial transmembrane potential in a caspase-independent manner, increase in H_2O_2 at higher concentrations	Cure colds, diarrhea, urinary tract infections, rheumatism, and skin problems, or reduce body weight.	[57]
52	*Inonotus obliquus* (Hymenochaetaceae)	Chaga	Polysaccharide	Increase in the colony-forming unit, granulocytes/macrophages, erythroid burst-forming unit, serum levels of IL-6 and TNF-α.	Antiparasitic, anti-tuberculosis, anti-inflammatory, and gastrointestinal properties	[58]
53	Haussknechtia elymatica (Apioideae)		Phenolics	Affects cellular components of the local immune reaction, including lymphocytes and/or monocytes recruited at the site of interaction, suppression of antigen processing, and presentation	Antioxidant	[59]

Table 2: Ongoing clinical trials in herbal plants for immunomodulatory effects

Ayurvedic plant	Health condition	Public Title	CTRI No.
Withania somnifera & *Tinospora cordifolia*	Breast cancer receiving chemotherapy	A clinical trial to study the effects of Ayurvedic formulation containing Ashwagandha and Guduchi in improving the quality of life in patients with breast cancer receiving chemotherapy as treatment	CTRI/2008/091/000052
Dioscorea bulbifera, Hippophae rhamnoides, Terminalia chebula, Terminalia arjuna & *Nardostachys jatamansi*	Metabolic syndrome	Prevention and management of Metabolic syndrome by a plant-based Ayurvedic formulation and prevention from coronary heart disease	CTRI/2014/12/005276
Psoralea & Asafoetida	White patches & leucoderma	A clinical trial to study the effects of two herbal formulations in patients with white patches on the skin (leucoderma).	CTRI/2011/07/001923
Eclipta Alba	Frontal Sinusitis	Sinusitis treatment with Ayurvedic medicine	CTRI/2013/05/003709
Withania somnifera	Immunomodulation	Effect of Ashwagandha on the Immunity of Healthy Participants	CTRI/2018/07/014792
Curcumin	Diseases of the respiratory system	Clinical Study to Evaluate the Efficacy and Safety of curcumin capsule in Patients with Cough Due to Chronic Bronchitis	CTRI/2018/12/016796
Aloe vera, Commiphora Myrrha, Saffron & *Rosa damascena*	Increasing immunity	A clinical trial to induce immunity and herd immunity against viruses including covid 19	CTRI/2021/02/031547

CONCLUSION

Many herbal plants have been employed as immunomodulatory that act through their main immuno-constituents in the form of polysaccharides, flavonoids, alkaloids, sterols, and terpenes. Immunomodulatory work by either stimulating or suppressing the immune system, and each has varying uses. These plants possess the significant therapeutic potential to lower the side effects and the high cost of other commercially available conventional modern drugs. Since very few of these plants have been studied and evaluated in the proper setting of clinical trials, future research of these drugs would prove to be beneficial.

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Authors do not have any financial or commercial conflicts of interest. All authors agree to submit the manuscript for publication. Hence, there is no conflict of interest among authors.

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All authors were equally involved in the design of the study, collection and analysis of the data, interpretation of the findings, and preparation and review of the manuscript. The corresponding author attested that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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