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REVIEW ARTICLE

Review on Chemical Constituents and Parts of Plants as Immunomodulators

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ABSTRACT

A substance that alters the immune response by augmenting or reducing the ability of the immune system to produce antibodies or sensitized cells that recognize and react with the antigen that initiated their production. Immunomodulators include corticosteroids, cytotoxic agents, thymosin, and immunoglobulins. Some Immunomodulators are naturally present in the body, and certain of these are available in pharmacologic preparations. Many botanical species have reported the immunomodulator activity. Immunomodulators are medications that weaken the body's immune system. The immune system is composed of immune cells and the proteins that these cells produce. These cells and proteins serve to defend the body against harmful bacteria, viruses, fungi, and other foreign invaders. Activation of the immune system causes inflammation within the tissues where the activation occurs. (Inflammation is, in fact, an important mechanism to defend the body used by the immune system.) Normally, the immune system is activated only when the body is exposed to harmful invaders. Immunomodulators decrease tissue inflammation by reducing the population of immune cells and/or by interfering with their production of proteins that promote immune activation and inflammation. Generally, the benefits of controlling moderate to severe ulcerative colitis outweigh the risks of infection due to weakened immunity. Examples of immunomodulator include azathioprine (Imuran), 6-mercaptopurine (6-MP, Purinethol), cyclosporine (Sandimmune), and methotrexate (Rheumatrex, Trexall).

Keywords: inflammation, immunomodulator, medication, augmenting.

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INTRODUCTION

Today's world is full of stress. Stress, basically is a reaction of mind and body against which have a significant impact on the immune response in general. The immune system is known to be involved in the etiology as well as pathologic mechanisms of many diseases. Immunology is thus probably one of the most rapidly developing areas of biomedical research and has great promises with regard to the prevention and treatment of a wide range of disorders [1].

Primary immunodeficiency diseases represent a class of disorders in which there is an intrinsic defect in the human immune systems (rather than immune disorders that are secondary to infection, chemotherapy, or some other external agent). In some cases, the body fails to produce any or enough antibodies to fight infection. In other cases, the cellular defenses against infection fail to work properly. There are more than 150 different primary immunodeficiency diseases currently recognized by the World Health Organization.[2]

Traditional and folklore medicines play an important role in health services around the globe [3]. In India around 20,000 medicinal plant species have been recorded recently but more than 500 Traditional communities use about 800 plant species for curing different diseases. Currently 80% of the world population depends on plant-derived medicine for the first line of primary health care for human alleviation because it has no side effects [4]. Plants are important sources of medicines and presently about 25% of pharmaceutical prescriptions in the United States contain at least one plant-derived ingredient. In the last century, roughly 121 pharmaceutical products were formulated based on the traditional knowledge obtained from various sources [5].

Immunostimulants or immunomodulators are drugs which enhance immune responses and can be used for the prevention or cure of some infective conditions and also in the management of cancers.

Immune Mechanism

Basically there are two different types of lymphoid cells, T and B cells which mediate 'cellular' and 'serologic' or 'humoral' immunity, respectively. Both these types of cells are present in the circulating blood and in peripheral lymphoid tissues. The recognition of the antigen by the T cells leads to proliferation of these cells, infiltration of immune cells at the site of action and cellular immunity. These reactions may be manifested as Delayed type Hypersensitivity, tissue graft rejection [6]. The other limb of immune system involving B cells is responsible for the genesis of specific antibodies immunoglobulins (IgA, IgD, IgE, IgM). The recognition of antigen (Ag) by the B cells leads to proliferation of these cells, conversion to plasma cells and generation of specific antibodies (Ab). The specific Ab binds with the specific antigen leading to its inactivation or even phagocytosis [7]. Phagocytic Activity by Nitroblue tetrazolium dye reduction assay, Lymphocyte Proliferation by mitogen

Immune Deficiency

Immune system protects against invading microorganisms, toxins and foreign cells. Immunodeficiency are as like Digeorge's syndrome due to lack of T cells (deficient cellular immunity), agammaglobinaemia due to lack of B cells (deficient humoral immunity) and Severe combined immunodeficiency disease (SCID) is due to adenosine deaminase deficiency causing death to T and B cells. AIDS is due to infection with HIV which causes depletion of CD₄⁺ T helper cells [8].

Mechanisms of Immunomodulation

Drugs may modulate immune mechanism by either suppressing or by stimulating one or more of the following steps

1. Antigen recognition and Phagocytosis
2. Lymphocyte proliferation/differentiation
3. Synthesis of antibodies
4. Antigen-antibody interaction
5. Release of mediators due to immune response
6. Modification of target tissue response/target effector organ
7. Complement system

Pharmacological Screening of Immunomodulators

Delayed type Hypersensitivity (SRBC)

Humoral Antibody Response to SRBC

Cyclophosphamide induced myelosuppression

Carbon Clearance test

Effect on Organ Weight

E.coli induced abdominal sepsis

Neutrophil Adhesion Test

Lymphocyte Production Test And Damage to Internal Organs

Plaque forming Cell Assay

Enzyme Linked immunoassay

Phagocytic Activity by Nitroblue tetrazolium

Future Scope

As immune system is known to be involved in the etiology as well as pathologic mechanisms of many diseases it has tremendously increased the need of drugs which are effective on immune system. To overcome the drawbacks of the synthetic immunomodulators there is a need of development of herbal immunomodulators. [9, 10]. This study will help the researchers to find out the new plants with immunomodulatory activity based on the parts used and their chemical constituents.

Plants with immunomodulatory activity are reported in detail below as per the parts used.

FRUITS

***Randia dumetorum* Lamk. (Rubiaceae) [11]**

Methanolic Extract of stem bark of *Randia dumetorum* Lamk. Belonging to family Rubiaceae was studied for the immunomodulatory activity. Along with methanolic extract methanolic extracts petroleum ether, chloroform, ethylacetate and methanol fraction were studied for Immunomodulatory activity. Immunomodulatory activity was evaluated using Humoral antibody (HA), Delayed type hypersensitivity (DTH) response and Cyclophosphamide-induced myelosuppression In vivo models with 50 & 100 mg/kg dose. This study revealed that methanolic extract showed slight increase in HA titre and other fractions showed insignificant effect. after 24 hrs. Methanol extract gave positive tests for alkaloids, phenolics, steroids, terpenoids, saponins, flavonoids and carbohydrates. In Ayurvedic texts, *R. dumetorum* is classified as a drug having properties similar to rasayanas and it was proved.

LEAVES

***Rubia cordifolia* L. (Rubiaceae) [12]**

Ethanol extracts of the leaves of *Rubia cordifolia* L. (Rubiaceae) (ERC) were investigated for their phytocompounds, in vitro and in vivo immunopharmacological properties. Immunomodulatory effects of this plant extract were proved in Cyclophosphamide (CP) - induced immunosuppressed animal models with 100 mg/ kg, b.w. dose and blood clotting assay were affected due to the suppressive effect of Cyclophosphamide. Administration of plant extract to CP- exposed animals resulted in enhanced immune responses. Responsible chemical constituents probably were alkaloids, cardiac glycosides, tannins, flavonoids and phenols as their presence was detected in ethanolic extracts. *Rubia cordifolia* L. was extensively used in traditional medicinal systems of India, China, Tibet, Nepal, and Sri Lanka for the treatment of various immune-related diseases and this was confirmed.

***Piper betel* L. (Piperaceae) [5]**

Methanolic extract of *Piper betel* leaves (MPb) was studied for immunomodulatory activity. Both in vitro as well as in vivo evaluation was carried out. Lymphocyte proliferation, interferon- γ receptors and the production of nitric oxide were measured in vitro with the dilutions 1:1000, 1:2000, 1:4000 and 1:8000. 125 mg / kg, 250 mg / kg, 500 mg / kg dose levels were studied in vivo for the humoral and cellular immune responses on mice immunized with sheep red blood cells. The study suggests possible immunosuppressive effect. The MPb was found to consist of mixture of phenols, flavonoids, tannins and polysaccharides and proves them as possible responsible chemical constituent for immunosuppressive activity. Thus, the

MPb could be explored extensively as a therapeutic agent to treat various immune disorders including autoimmune disorders.

***Morus alba* Linn. (Moraceae) [13]**

Methanolic extract of *Morus alba* leaves was evaluated for their effect on immune system by using different experimental models such as carbon clearance test, cyclophosphamide induced neutropenia, neutrophil adhesion test, effect on serum immunoglobulins, mice lethality test and indirect haemagglutination test. Methanolic extract of *Morus alba* was administered orally at low dose and high dose of 100 mg/kg and 1 g/kg respectively and *Ocimum sanctum* (100 mg/kg, po) was used as standard drug. *Morus alba* increases both humoral immunity and cell mediated immunity. The belief as per traditional medicine that mulberry leaves possess immunomodulatory activity was confirmed.

***Aesculus indica* (Sapindaceae) [14]**

Aqueous extract of *Aesculus indica* was evaluated for immunomodulatory activity in rats. The assessment of immunomodulatory activity was carried out by testing the humoral (antibody titre) and cellular (foot pad swelling) immune responses to the antigenic challenge by sheep RBCs and by neutrophil adhesion test. On oral administration of 50 and 100 mg/kg of the extract, a significant increase in neutrophil adhesion and delayed type hypersensitivity response whereas the humoral response to sheep RBCs was unaffected. The study concluded that *Aesculus indica* showed a significant stimulation of the cell mediated immunity and no effects on the humoral immunity due to the presence of proteins, flavonoids, alkaloids, steroids and phenolic substances.

SEEDS

***Nigella sativa* (Ranunculaceae) [15]**

Ethanol extract of *Nigella sativa* was studied for immunomodulatory activity. *Nigella sativa* is commonly known as black cumin seed. Alkaloids were isolated from *N. sativa* seeds viz. nigellidine, nigellimine, and nigellicine and their pharmacological actions have not been reported. Lymphocyte-activation assay was studied to determine Immunomodulatory activity. Column fraction-5(CC-5) had no stimulatory effect on mouse splenocytes as such. CC-5 and water fraction, however, enhanced the proliferative response in the presence of ConA (3 µg/ml), but not LPS (1 and 6 µg/ml). These data indicate that CC-5 possesses a potent cytotoxic effect as well as a potentiating effect on the cellular immune response. The present results yielded an incomplete picture on the effects of the extracts on the immune system, we have demonstrated that the extract per se does not have any immunomodulatory activity, but in the presence of optimal doses of mitogen there is a significant potentiation of the immune response. The mechanism whereby it produces this needs to be resolved.

FLOWERS

***Tanacetum vulgare L. Compositae (Asteraceae)* [16]**

Aqueous extract of *Tanacetum vulgare* florets consisted of four polysaccharide. Their isolation and purification was carried out by the sequential use of hot-water extraction, ethanol precipitation, ultra-filtration, anion-exchange, and size-exclusion chromatography. This fraction was tested for innate immune cell function using Analysis of NF- κ B activation, Analysis of NO production, Analysis of ROS production, Determination of TNF- α , Cytotoxicity assay, Complement fixation assay and Determination of myeloperoxidase (MPO) activity. The active constituents responsible for activity were flavonoids and terpenoids and polysaccharides. It also consisted of Sugars such as galacturonic acid, galactose, arabinose, and rhamnose. Results provided a molecular basis to explain at least part of the beneficial therapeutic effects of *Tanacetum vulgare* extracts, and support the concept of using *Tanacetum vulgare* polysaccharides as an immunotherapeutic adjuvant.

ROOTS***Chlorophytum borivilianum (Liliaceae)* [17]**

Ethanol extract of the roots of *Chlorophytum borivilianum* belonging to family Liliaceae was evaluated for immunomodulatory activity. Models used were Non-Specific Immunity Determined by Survival Rate against Fungal Infection, In Vivo Phagocytosis Using Carbon Clearance Method, SRBC-Induced Delayed-Type Hypersensitivity Reaction (DTH Response) and Activity Against Drug-Induced Immunosuppression. Effective dose was 200 mg/kg dose when compared with 100mg/kg of sapogenin as a standard. Immunostimulant activity of ethanolic extract was more pronounced as compared to sapogenins. The results, thus justifies the traditional use of *C. borivilianum* as a rasayana drug.

***Ficus benghalensis (Moraceae)* [18]**

Successive Methanolic extract (SME) of aerial roots of *Ficus benghalensis* (Family Moraceae) was studied for immunomodulatory activity. Various extracts of the aerial roots of *Ficus benghalensis* were evaluated for potential immunomodulatory activity, using the in vitro polymorphonuclear leucocyte (human neutrophils) function test, using rats as the animal model, using sheep red blood cells (SRBC) as the antigen and Distilled water served as a control in all the tests. In vitro all the extracts were evaluated at concentrations of 0.5, 1.0 and 2.0 mg/ml. For invivo studies dose of 50, 100 and 200 mg/kg were used. It was concluded that the presence of steroids and flavonoids in the petroleum ether, benzene and chloroform extracts. The acetone, methanol and water extracts were found to contain flavonoids, phenolics, steroids, glycosides, carbohydrates and proteins which are the responsible chemical constituents for activity. The SME of *Ficus benghalensis* was found to have a significant immunostimulant activity on both the specific and non-specific immune mechanisms.

***Heracleum nepalense D. Don (Apiaceae)* [19]**

Methanolic extract of *H. nepalense* roots were assessed for immunostimulatory activity, using different in vitro and in vivo experimental models. The immunostimulatory potential of the test compound was investigated by in vitro, phagocytic index and lymphocyte viability tests, using interferon α -2b, a known immunostimulant drug, as the standard. Other tests such as carbon clearance, antibody titer and delayed type hypersensitivity were studied in mice, using levimasole as the standard. The dried root extract (1000 μ g/ml) and isolated quercetin glycoside (50 μ g/ml) significantly increased the in vitro phagocytic index and lymphocyte viability in all assays. There was a significant increase in antibody titer, carbon clearance and delayed type hypersensitivity in mice. *H. nepalense* exhibited a dose-dependent immunostimulant effect, which could be attributed to the flavonoid content or due to the combination with other component(s).

BARK

Cinnamomum zeylanicum (Lauraceae)

Cinnamomum zeylanicum bark (Lauraceae) commonly known as cinnamon suspension in distilled water with 0.5% sodium carboxy methyl cellulose was used to study the immunomodulatory activity using different experimental models such as carbon clearance test, cyclophosphamide induced neutropenia, neutrophil adhesion test, effect on serum immunoglobulins, mice lethality test and indirect haemagglutination test. *Cinnamomum zeylanicum* bark contains about 0.5 -10% of volatile oil, 1-2 % of tannins (Phlobatannins), mucilage, calcium oxalate, starch and sweet substance in the form of mannitol. Presence of Tannins might be responsible for the proposed activity. Immunomodulatory activity was investigated in 10 mg/kg/po and 100 mg/kg/po dose concentration. Levamisole (2.5 mg/kg p.o) was used as standard drug. It was concluded that cinnamon in high doses stimulated both cellular and humoral immunity and at low dose, increased only the non-specific serum immunoglobulin levels.

Miscellaneous Plants

Several other plants species that have utility in immunomodulatory therapy have also been reported in the literature. Some of these plants like *Couropita guianensis*, *Withania somnifera*, *Ocimum sanctum*, *Mucuna Pruriens*, *Trapa bispinosa*, etc. are the plants reported with immunomodulator potential. Some plants with immunomodulatory activity with the major parts used, chemical constituents responsible for the activity and more frequently used models are summarized in the Table 1. [3,20,21,22].

Table 1 List of Plants investigated pharmacologically for Immunomodulatory activity.

Botanical Source	Extract Used	Dose	Chemical constituent	Animal model	Conclusion
<u>FLOWERS</u>					
<i>Couropita guianensis</i> (Lecythidaceae) [3]	Methanol	100-200 mg/kg	Steroids, Phenolics, flavonoids, glycosides, carbohydrates and proteins	Invivo -Hypersensitivity Reaction, Hemagglutination Reaction using SRBC's Invitro - Phagocytosis of <i>Candida albicans</i>	Immunostimulant activity on both specific and non-specific immune mechanisms
<i>Hibiscus sabdariffa</i> (Malvaceae) [23]	Aqueous alcoholic	WF 100 mg/kg EF 50-100mg/kg	---	Invivo - Hemagglutination Tets, Cytokine determination	Immunostimulatory activity with increase in production of Anti-inflammatory cytokine, IL-10 and reduction in tissue necrosis factor -alpha
<i>Azadirachta indica</i> (Meliaceae) [24]	Aqueous	200 & 400 mg/kg	---	Invivo - Carbon Clearance test, Cyclophosphamide induced myelosuppression, Humoral Antibody Response to SRBC, Delayed Type Hypersensitivity Invitro - Nitric Oxide Assay, Superoxide Assay Reduction	Stimulates both specific and nonspecific immune responses. Potent immunostimulant against cytotoxic drugs
<u>ROOTS</u>					
<i>Withania somnifera</i> (Solanaceae) [25]	Methanol	100 mg/kg, 20 mg/kg	Steroidal Lactones (Withanolides), Polysaccharides, lectins, Proteins and peptides	Invivo - Drug induced Myelosuppression, Effect on Organ Weight, Bone marrow cellularity & α -esterase positive cells, Antibody titre, Delayed Type of Hypersensitivity, Phagocytic activity of macrophages	Immunomodulator to counteract undesirable effects of myelosuppressive drugs. Stimulates the haemopoietic system and also enhances the differentiation of stem cells.

Botanical Source	Extract Used	Dose	Chemical constituent	Animal model	Conclusion
<i>Boerhavia diffusa</i> (Nyctaginaceae) [26]	Ethanol	100 mg/kg	Alkaloids, carbohydrates, glycosides, triterpenoids, steroids, phenols and tannins	Invivo - Carbon Clearance Assay Delayed Type Hypersensitivity Test	Roots possess antistress, adaptogenic and immunopotentiating activity
<i>Calophyllum brasiliense</i>	Methanol	10,50,100 & 200	---	Invitro – Lymphocyte Proliferation Assay	Immunostimulant

(Clusiaceae) [27]		mg/kg			
<i>Clerodendrum phlomidis</i> [28]	Methanol	300 mg/kg	B-sitosterol & γ -Sitosterol, Cetyl alcohol, Clerodin, Clerosterol, Clerodendrin, Flavonoids-Pectolinarigenin, Hispidulin, Apigenin, luteolin	Invivo - Haemagglutination Antibody Titre, Plaque forming Cell Assay Delayed Type Hypersensitivity Response, Carbon Clearance Test, E.coli induced abdominal sepsis	Immunomodulator (Higher response to specific immunity as compared to non specific immunity)
<i>Premna integrifolia</i> [28]	Methanol	300 mg/kg	Premnine, Ganikarine, Premnazole, Flavonoids, luteolin, sterols and terpenes	Invivo - Haemagglutination Antibody Titre, Plaque forming Cell Assay Delayed Type Hypersensitivity Response, Carbon Clearance Test, E.coli induced abdominal sepsis	Immunomodulator (Higher response to specific immunity as compared to non specific immunity)
<i>Baliospermum montanum</i> (Euphorbiaceae) [29]	Alcoholic	25, 50 & 100 μ l/ml	Tannins, Saponins, Flavonoids, Glycosides	Invitro - Phagocytosis Neutrophil Locomotion and Chemotaxis, Immunostimulant studies by Slide method, Nitroblue tetrazolium Test	Immunostimulant

Botanical Source	Extract Used	Dose	Chemical constituent	Animal model	Conclusion
LEAVES					
<i>Ocimum sanctum</i> (Lamiaceae) [20]	Aqueous	50,100,250 ,500,1000 μ g/ml	Ascorbic acid and flavonoids	Invitro - Nitroblue tetrazolium Test, Phagocytosis of <i>Candida albicans</i> , Candida cidal assay, Neutrophils locomotion & Chemotaxis	Ascorbic acid and flavonoids isolated from the leaf possess potent immunostimulant activity, but in combination showed synergistic activity it might be due to antioxidant property.
<i>Aloe vera</i> (Liliaceae) [30]	Ethanol	150 & 300 mg/kg	---	Invivo - Effect on Total WBC, Effect on Antibody Production, Effect on Plaque forming Cells, Effect on the phagocytic activity of Peritoneal macrophages	Potential candidate in several immunosuppressed clinical conditions
<i>Cassia auriculata</i> (Caesalpiniaceae) [31]	Ethanol	50 &100 mg/kg, 100 & 200 mg/kg	Pet. Ether extract-steroids Alcoholic & Aqueous Extract-Alkaloids, Flavonoids, Tannins, Phenolics	Invivo - Humoral Antibody Titre, Delayed Type Hypersensitivity Response Neutrophil Adhesion Test	Significant immunostimulant effect on cell mediated immunity and no effect on Humral immunity
<i>Tridax procumbens</i> (Compositae)[32]	Ethanol	250 mg/kg	Flavones, Glycoside, Polysaccharide, Monosaccharide, Asteraceae	Invivo - Lymphocyte Production Test And Damage to Internal Organs	Stimulatory effect on humoral immunity and stimulated phagocytosis and offered protection against <i>P. aeruginosa</i> infection

SEEDS					
<i>Mucuna Pruriens</i> (Fabaceae) [21]	Ethanolic	100 & 200 mg/kg	---	Invivo -Humoral Antibody Response to SRBC, Delayed type Hypersensitivity (SRBC) , Neutrophil Adhesion Test	It produces inhibitory effect and suggests its use in inflammatory disorders.
<i>Botanical Source</i>	Extract Used	Dose	Chemical constituent	Animal model	Conclusion
FRUITS					
<i>Trapa bispinosa</i> (trapaceae) [22]	Aqueous	50, 100 & 200 mg/kg	Alkaloids, carbohydrates, starch, tannins, phenolic compounds & saponin glycosides	Invivo - Delayed type Hypersensitivity (SRBC) , Humoral Antibody Response to SRBC, Carbon Clearance test, Neutrophil Adhesion Test	Promising immunostimulatory activity
<i>Terminalia belerica</i> (Combretaceae) [33]	Methanol	0.1,1,10,50 & 100 µg/ml	Gallic acid, ellagic acid, ethyl gallate, chebulic acid, β-sitosterol, 3-lignans & one flavan	Invivo - Phagocytic Activity by Nitroblue tetrazolium dye reduction assay, Lymphocyte Proliferation by mitogen induced splenocyte proliferation assay, Invitro – Phagocytic index by cellular lysosomal enzyme activity assay.	<i>T. belerica</i> shows immunosuppressant effect at low concentration while stimulatory activity at high concentration
BARK					
<i>Alstonia boonei</i> (Apocynaceae) [34]	Pet. Ether, Ethyl acetate, Diethyl ether, Ethanol	25 & 50 µl/well	Alkaloids – Indole, terpenes, lactones & Steroids, Triterpenes – a & b ammyrin & lupeol	Invitro – Haemolytic Assay, Chemiluminescence Assay	Anticomplementary action may be beneficial in rheumatoid arthritis.
<i>Acacia catechu</i> (Leguminosae) [35]	Aqueous	5 & 50 mg/kg	Catechin and epicatechin	Invivo - Neutrophil Adhesion Test, Mice Lethality Test, Carbon Clearance Assay, Cyclophosphamide Induced Nuetropenia, Serum Immunoglobulin Levels, Indirect Haemagglutination Test	The aqueous extracts of Acacia catechu have significant effect on both the cell mediated and the humoral immunity. Low dose was more effective as compared to the higher dose.
<i>Botanical Source</i>					
<i>Bauhinia variegata</i> (Caesalpiniaceae) [1]	Ethanol	250 & 500 mg/kg	tannins, steroids, alkaloids, flavonoids, β sitosterol, lupeol, vitamin C, kaempferol,	Invivo - Humoral antibody (HA) response, Carbon Clearance test and Neutrophil Adhesion test	Immunostimulant activity on both specific and non-specific immune system

			flavones, quercetin & saponins.		
<i>Matayba elaeagnoides</i> (<i>Sapindaceae</i>) [27]	Methanol	10,50,100 & 200 mg/kg	---	Invitro – Lymphocyte Proliferation Assay	Immunostimulant
AERIAL PARTS					
<i>Alternanthera tenella</i> <i>Colla</i> (<i>Amaranthaceae</i>) [36]	Aqueous	5 & 50 mg/kg	Fatty acids, flavonoids, polysaccharides, triterpenes, Glycosides & saponins	Invivo - Antibody Assay, Antitumor activity, Body and lymphoid organ weight, Splenic cellularity, Plaque Forming Cell Assay, Enzyme Linked immunosorbant Assay	Inhibitory action on B-lymphocyte fuction, Reduce antibody production to T-dependent antigen, Simultaneous immunostimulatory and immunosuppressive activity
<i>Hyptis suaveolens</i> (<i>Lamiaceae</i>) [37]	Alcoholic	75 mg/kg	Volatile Oil	Invivo - Pyrogallol induced myelosuppression, Humoral Immune Response	Immunostimulant
<i>Dittrichia viscose</i> (<i>Asteraceae</i>) [38]	Succe-ssive extraction	100 – 1000 µg/ml	Flavonoids	Invitro – Cell Proliferation Assay, Cytotoxicity Assay, Brine Sheep Test	Immunomodulatory effect
<i>Aster squamatus</i> (<i>Asteraceae</i>) [38]	Succe-ssive extraction	100 – 1000 µg/ml	Flavonoids	Invitro – Cell Proliferation Assay, Cytotoxicity Assay, Brine Sheep Test	Immunomodulatory effect
<i>Glebionis coronaria</i> (<i>Asteraceae</i>) [38]	Succe-ssive extraction	100 – 1000 µg/ml	Flavonoids	Invitro – Cell Proliferation Assay, Cytotoxicity Assay, Brine Sheep Test	Immunomodulatory effect

Botanical Source	Extract Used	Dose	Chemical constituent	Animal model	Conclusion
<i>Calendula arvensis</i> (<i>Asteraceae</i>) [4]	Succe-ssive extraction	100 – 1000 µg/ml	Flavonoids	Invitro – Cell Proliferation Assay, Cytotoxicity Assay, Brine Sheep Test	Immunomodulatory effect
<i>Carlina involucrate</i> (<i>Asteraceae</i>)	Succe-ssive extraction	100 – 1000 µg/ml	Flavonoids	Invitro – Cell Proliferation Assay, Cytotoxicity Assay, Brine Sheep Test	Immunomodulatory effect
<i>Galactites tomentosa</i> (<i>Asteraceae</i>)	Succe-ssive extraction	100 – 1000 µg/ml	Flavonoids	Invitro – Cell Proliferation Assay, Cytotoxicity Assay, Brine Sheep Test	Immunomodulatory effect
<i>Inula crithmoides</i> (<i>Asteraceae</i>)	Succe-ssive extraction	100 – 1000 µg/ml	Flavonoids	Invitro – Cell Proliferation Assay, Cytotoxicity Assay,	Immunomodulatory effect

				Brine Sheep Test	
<i>Leontodon tuberosus</i> (Asteraceae)	Succe-ssive extraction	100 – 1000 µg/ml	Flavonoids	Invitro – Cell Proliferation Assay, Cytotoxicity Assay, Brine Sheep Test	Immunomodulatory effect
<i>Reichardia picroides</i> (Asteraceae)	Succe-ssive extraction	100 – 1000 µg/ml	Flavonoids	Invitro – Cell Proliferation Assay, Cytotoxicity Assay, Brine Sheep Test	Immunomodulatory effect
<i>Sonchus oleraceus</i> (Asteraceae)	Succe-ssive extraction	100 – 1000 µg/ml	Flavonoids	Invitro – Cell Proliferation Assay, Cytotoxicity Assay, Brine Sheep Test	Immunomodulatory effect
WHOLE PLANT [4]					
<i>Ipomea pes-caprae</i> (Convolvulaceae)	Methanol	10,50,100 & 200 mg/kg	---	Invitro – Lymphocyte Proliferation Assay	Immunostimulant

CONCLUSION

A variety of botanical products have been reported to possess immunomodulatory activity. The documented literature has centred primarily on pharmacological action in experimental animals. Except for a few phytogenic compounds, limited clinical data are available to support the use of herbs as immunomodulatory agents and thus, the data on efficacy and safety are limited. Despite this, there are several botanical products with potential therapeutic applications because of their high efficacy and low toxicity. Review also focuses the use and reliability of models for assessing the immunomodulatory activity. Finally, it should be noted that substances such as flavonoids, tannins, polysaccharides, alkaloid, Fatty acids, glycoside, terpenoid, steroid, saponin and many others, that possess immunomodulatory activity and Humoral Antibody Titre, Delayed Type Hypersensitivity Response, Neutrophil Adhesion Test, Lymphocyte Proliferation Assay and Carbon Clearance Test are the most frequently used models for immunomodulatory screening.

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