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Review Article

Potential Role of Medicinal Plants for their Immunomodulatory Activity - A Review

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Abstract

Immunomodulation is basically a process that can alter the immune system of an organism by interfering with its functions. The current approach is to know about the medicinal plants that are biologically active and could potentially be of help in the development of modern and new immunomodulating agents. As in modern-day life, extensive exposure to industry-based pollutants/xenobiotics has resulted in the emergence of a variety of immune deficiencies or hypersensitivity situations, where immunology can play an important role.

The inference results in either immune-stimulation, an enhancement of immune reactions, or immune-suppression imply mainly to reduce resistance against infection, stress which may be because of environmental or chemotherapeutic factors. Bioactive natural products provide the excellent raw material for the discovery and development of novel immune-modulatory compounds.

A good number of bioactive natural products used as medicinal plants have stood the test of time, particularly for the treatment of allergic metabolic and degenerative diseases associated with aging. These bioactive natural products are believed to promote positive health and maintain organic resistance against infections by reestablishing body equilibrium and conditioning the body tissues. A large variety of natural bioactive plants mentioned in Ayurveda for their immunomodulation, adaptogenic and rejuvenating properties have been under study.

Keywords: Immunomodulation; Antigen specific immune response; Non-specific immune response

Introduction

Historical period documents medicine and botany hand-in-hand in service of mankind. Bioactive medicinal plants have been and are still in use by the practioners of the traditional system of medicine. According to WHO survey of 1993, 90% of patients are still treated by using bioactive medicinal plants/plant extracts in Bangladesh, 85% in Burma, 80% in India, 75% in Nepal, 65% in Sri Lanka and 60% in Indonesia and Pakistan respectively. In India medicinal plants endowed with leads from Ayurveda, Siddha and Unani have been used with success in the management of various diseased conditions. Claims made about these drugs are basically their safety besides being effective and economical [1].

Ayurveda, the Indian system of medicine deals with plant drugs, the main stress being on strengthening body's own defense system. The concept of "Rasayana" was put forth in Ayurveda, meaning a group of plants with potential to treat body's main defense system. This documented use of herbal medicinal plants and the concept of immune system came in India with Ayurveda (Graph 1).

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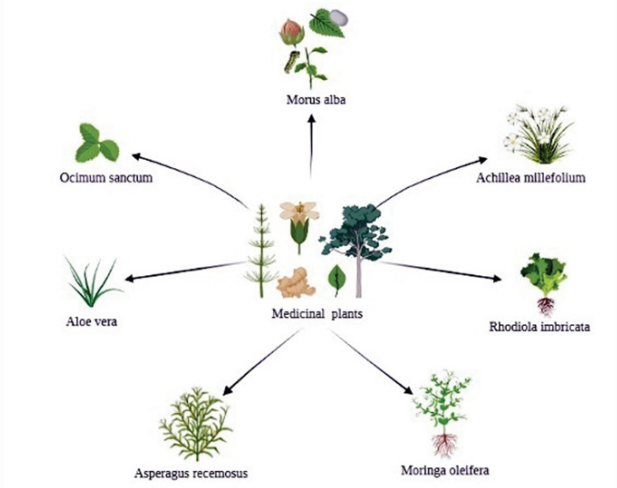
Plants extracts are being used in Europe for rejuvenating therapy and treatment of chronic disorders. These have been shown to possess immunostimulatory activity [2,3] have described plants with immunostimulatory activity in India and China. Plants with above activity have also been documented by Dua et al. [4] and Nadkarni et al. [5]. Herbals are known to bring general improvement in the homeostasis. Plants have been reported to have regulatory effects on



Graph 1: Graphical abstract represent the function of medicinal plant and their plant derived immunomodulators.

immunity, endocrine, neural and cardiovascular systems [6]. Certain bioactive herbals have been suggested to act through modulation of these systems and are effective against some auto-immune diseases [7]. On the contrary they have actually been contributing to the modern medicine, e.g., morphine, quinine, reserpine, atropine, vincristine, and vinblastine [6].

Study of the defense system of the body is in vogue and has evoked great interest recently. The balance has shifted to a greater extent from simple treatment of symptoms to the basic understanding of immunology of disease states. This study has been designated as science of immunology. Immunology is not only the most rapidly developing area of biomedical research but also possess great promise of being the major advance in the prevention and treatment of wide range of chronic disease [8]. Arthritis, ulcerative- colitis, asthma, allergy, vitiligo and many more parasitic and infectious diseases are now primarily considered is immunological disorders. Disturbance of immune mechanisms have been reported to be involved in a variety of other metabolic diseases such as diabetes mellities, cancer, atherosclerosis myocardial disorders and cirrhosis [9].

Modulation of immune response as a basis of therapy has been of interest since many years. First scientific report was put forth by Lazarev in 1947 [6], who demonstrated the capacity of diabazol to increase non-specific resistance. This compound possessed adaptogenic activity which was supported by Anosov and Lazarev. Development of a series of synthetic compounds followed the impact being on to utilize these to balance immune system.

Synthetic drugs named as Cyclophosphamide (alkylating agents), 6-mercaptopurine (pure antagonists, methotrexate (folic acid antagonists), 5-fluorouracil (pyrimidine antagonists) and adramycin [10-12]; are some of the examples. Designing of any immunomodulator requires on the onset and in depth understanding of various components of immune system. An attempt has been made here to give a bird's eye view of some important components of this complex system. Immune response includes both antigen specific and antigen non-specific processes.

Antigen specific immune response (Protective host defense mechanism)

The basic requisite of the immune system of the body is to recognize and destroy the "Non Self" which includes protection against various infections maintaining homeostasis and immune surveillance [13]. Components involved in the immune response can be classified under two major components i.e. molecular or humoral and the cellular factors. Antigen specific immune responses are represented through T-lymphocytes (T-cells) capable of activating B-lymphocytes which are then triggered by antigens to become plasma cells, secreting antibodies. Immunoglobulins IgM, IgG, IgA, IgD, IgE and their subclasses are also produced by B-cells. T cells play a significant role in the interaction of B-cells with macrophages. Cellular immunity is functionally related to the immune activity of cells, particularly the T-cells, whereas the humoral immunity emphasizes the production of B-cells or antibodies. During the immune response to a particular antigen the production of antibodies by B-cells is governed by following possible mechanisms; (a) humoral immunity, (b) a temporary loss of reactive B-cells (c) T-suppressor action directly on B-cell differentiation and (d) indirect T- suppressor action on T-helper cells [14]. The mechanism of action of specific antibodies inhibits the production of antibody of the same specificity by feedback control system [15].

Antibodies are generally operative against bacteria or bacterial products, whereas cellular reactivity works against viral and other micro-organisms thus showing protective effect against infections thereby enhancing the immunity. Hence immune reactions of both humoral and cellular types play an important role in the defense of the host against infections.

Immune memory

In order to develop an immune response characterized by antibody synthesis, the participation of two types of lymphocytes (T & B-Cells) is necessary. Other types of lymphocytes and their metabolic products i.e. lymphokines or Interleukins (ILS) and Natural Killer cells (NK) function as messengers. The messengers are carried to other lymphocytes, phagocytes or non-immune cells to produce immune responses. Macrophages both inactive and active remain essentially the same [16]. To begin an immune response immunologically competent lymphocytes with receptors must make contact with antigen. Starting from the response to antigen till the final product antibody is synthesized we can observe an amazing specificity. This specificity is revealed by the capacity of antibody to react against a particular determinant of an antigenic molecule. The antibody to a particular antigen is so exquisitely specific that even minor alterations in the determinant molecule or the portion responsible for its antigenic reactivity markedly alter the response.

Non-specific immune response

Prominent function of non-specific immune response is through activation of complement cascade which potentiates the macrophages in the process of ingesting foreign material (antigen) without the usual aid of immunoglobulin or antibody synthesis. Macrophages and neutrophils engulf almost anything. Polymorph Nuclear Leucocytes (PMNL), mononuclear phagocytes and macrophages are part of above mentioned non-specific immune system. These components function by the production of Reactive Oxygen Species (ROS) by activated PMNL. C3 component of complement is found to mobilize leucocytes *in vitro* and *in vivo* promoting leukocytosis factor [17,18].

Immune regulation- cell interaction

Interaction between different components of immune system leads to consecutive efforts to prevent the diseased conditions. In totality the functional interactions between an antigen non-specific and antigen specific (humoral & cellular) components of immune system are manifold, intensive and intimate. For instance macrophages and lymphocytes interact through the phenomenon of antigen dependent action. Macrophage processed antigen is presented to T-lymphocytes. In this process cell to cell contact takes place, macrophage and lymphocytes interacting in the process of immune response share histocompatibility linked gene products. The macrophage seems to select discrete regions of the antigen molecule for recognition by sensitized T-cells [19-21]. Other cells involved in this response are activated monocytes and macrophages producing monokines that interact with lymphocytes.

The involved mediator cells e.g. mast cells, basophils, eosinophils and platelets release soluble mediators such as chemotactic factors, platelet activating factors, heparin, prostaglandins and leukotrines which in turn are responsible for inflammatory manifestation following an immune reaction [22-27]. Phagocytes are also activated by leukocytes through this process to perform phagocytosis. It is very clear that any immune response is brought about through functional interactions of the different components of the immune system.

Antigen non-specific and antigen specific processes are closely and interdependently linked in a regulatory network of the immune response. Besides this direct cell to cell contact, macrophages and lymphocytes influence individual functions indirectly also.

Such interaction are mediated through secretions of cytokines i.e. monokines (IL-1) and lymphokines that provoke specific activities resulting in lymphocyte proliferation. Lymphokines produced by T-lymphocytes designated as IL-2 activate macrophages. The above described activation of macrophages leads to enhance phagocytosis, microbial killing through secretary activities due to adherence of foreign molecules to macrophageal surface. Lymphokines such as IL-5 are known to have released chemotactic effects on eosinophils, basophils and neutrophils at the site of inflammation.

Activated T-lymphocytes also produce IL-4, a lymhokine that stimulates B-cells to produce antibodies. In cases of allergic or inflammatory reaction the antibody (IgE) produced would trigger mast cells to release inflammatory mediators including histamine, prostaglandin D-2 (PGD2) and leukotrine C-4 (LTC4). Together with basophils mast cells play a key role in immediate hypersensitivity and other allergic manifestations. The picture given above of the functional interactions between cellular and humoral immuno-factors is far from complete. Still, it illustrates however the interdependency of regulatory and effector cells, their molecular messengers and the mediators in the antigen specific and the antigen non-specific immune response. Interaction of various immune components and relevant non immune cells results in correction of immune system [28].

Immunomodulation

Immunomodulation is basically a process which can alter the immune system of an organism by interfering with its functions. This interference results in either immunostimulation, an enhancement of immune reactions or immunosuppression which imply mainly to reduce resistance against infections stress that may be because of environmental or chemotherapeutic factors [6]. Immunostimulation and Immunosuppression both are needed to be tackled depending on the type of immunological disturbance. Hence immunostimulating and immunosuppressing agents have their own standing. Recently search for better moieties with the activities is becoming the field of major interest. Research focused on the development of immunomodulators is directed towards activities that can be expressed in terms of stimulation or inhibition of immunofactors and their integrated function [28]. Apart from specific stimulative or suppressive activity certain agents have been shown to process activity to normalize or modulate the pathophysiological processes in the underline immune response and hence the term immunomodulation or immunomodulatory agents are now used [29]. This activity varies with dose level and most of the immuno-suppressants show immunostimulation at low doses [30]. Most of the chemical agents which are fairly known to have effect on immune system are immunosuppressants and cytotoxic agents [31]. Azathioprine and cyclophosphamide have been extensively studied as standard immunosuppressors. Azathioprine inhibits DNA synthesis and has antinflammatory activity by virtue of its effects on IFN and monocyte production although the immunopharmacology of this non-specific agent is not well understood even today.

Cyclophosphamide importance and safety is not well established [6]. The other group of drugs described and worked in immunopharmacology is immunostimulant mostly derived from natural resources. Levamisole the earlier anti-parasitic drug now has been identified as immunomodulator and has been studied in a number of diseases including rheumatoid arthritis where it reduced rheumatoid arthritis factor titers [32]. As described above immunomodulation represents an important therapeutic approach in the treatment of various diseases. Immunomodulators so for available have been categorized on the basis of their origin as under.

Biological origin:

- Products of immune system: Thymic hormones, Thymosine, Thymopoietin, FTS, Lymphokines, Lymphokines nonpurified, Interferon, Interleukine-2, others Tuftsine, Bacterial preparations, Bacillus Calmette Guerin (BCG), *Brucella abortus, Corynebacterium parvum, Pseudomonas aeruginosa, Bordetella pertussis, Nocardia.*
- Chemically identified bacterial extracts: *M. smegmatis, K. pneumonia, M. tuberculosis.*
- Chemically identified compounds from fungi: Krestin, Glucan, Lentinan, Cyclomunine, Bestatin.

Natural products or their analogs: Vitamin A and its derivatives, Vitamin E, Lysolecithin, Lynesterol, Synthetic Compounds, Sulfur-containing compounds, Levamisole, Diethyldithiocarbamate, Cimetidine.

Compounds with a nucleotide: Poly A: U, Poly I: C, Isoprinosine, and NTP 15392.

Other miscellaneous compounds: Azimexon, Therafectin, Tilorone, Indomethacine.

With the discovery of numerous immunomodulators and a good deal of information about their mechanisms of action, great hopes have arisen envisaging that in the future, we shall be able to modulate the complex immune system into desired direction [33].

Natural product resources and their selection

Synthetic compounds although very effective in controlling different components of immune system have inherent severe side effects. However, almost limitless resources are provided by the plethora of potential medicinal plants, for the treatment of a variety of disorders including disturbed immune system. It has now become possible to analyses that extracts from reputed plants can prove to be beneficial immunologically with availability of various *in-vitro* and *in-vivo* testing models. This motivation has to be pursued to search for new and better drugs from plant resources [28].

Immunopharmacological studies have been carried out in the recent past on large number of plants. The most notable amongst them are enumerated below

***Acanthopanax obovatus* hoo (Arallaceae):** *A. obovatus* is a Chinese traditional herb being used as a tonic. Polysaccharide isolates AOPS from this plant has shown immunomodulatory activity. Administration of this fraction resulted in increase in the weight of the spleen and the number of cells. This isolate augments the phagocytosis of peritoneal macrophages both in normal and immune suppressed mice [34]. In a haemagglutinin assay AOPS increased the production of specific antibodies and antagonized the suppressive effect of cyclophosphamide in all the parameters under study. Enhancement in the degree of *in vitro* spleen cell mediated red Blood Cells (SRBC) hemolysis was observed [34] on administration of AOPS.

***Althea officinalis* L (Malvaceae):** A complex mucous polysaccharide isolated from *Altheia officinalis* has been shown to enhance phagocytosis [35].

***Aconitum heterophyllum* Wall (Ranunculaceae):** *A. heterophyllum* has been used in folklore medicine in giardiasis and as an anti-diarrhoel [36,37]. Ethanolic extract (95%) of bark has been reported to stimulate phagocytosis and inhibit the humoral immune response against SRBC in mice [38]. It has shown 35% to 50% inhibitory activity against *S. lutea* and a large variety of organisms tested [39].

***Abutilon indicum* L (Malvaceae):** Dried powdered material of *A. indicum* has been reported to increase the humoral antibody response to *Salmonella typhimurium* antigen in rabbits. Survival time of rabbits against virulent *Staphylococcus aureus* challenge increases on administration of *A. indicum* [40].

***Allium cepa* L (Lilliaceae):** Handa et al. [41] have shown the bronchodilatory effect of the chloroform fraction of the cold 95% ethanolic extract of *Allium cepa* and *quercetin.*

***Arctostaphylos uva-ursi Spreng.* (Ericaceae):** Methanolic extract (50%) (U–Ext) from *A. uva-ursi* leaf given orally (100 mg/kg) showed an inhibitory effect on the swelling induced by Picryl Chloride (PC-CD). The inhibitory effect was enhanced when u -ext and prednisolone was used in combination [42]. *Arbutin* isolated from the leaves of *A. uva-ursi* plus indomethacin showed inhibitory effect on the swelling induced by PC-CD and SRBC stronger than that of indomethacin alone [43].

***Aristolochia clematitis* L (Aristolochiaceae):** Aristolochic acid isolated from *A. clematitis* has been shown to enhance the phagocytic function of leucocytes and peritoneal macrophages [44]. It has been reported to prevent the prednisolone induced reduction of rosette forming cells and check chloramphenicol and tetracycline induced reduction of phagocytosis. It has been reported to be carcinogenic [45,46] for which reason the drug containing this compound have been withdrawn from the market.

***Arnica Montana* L (Compoitae):** *Arnica Montana* is widely used externally in traditional medicine in Europe and North America because of its anti-inflammatory and anti-microbial activity. Immunostimulant properties of crude polysaccharide from the herb have been described [47]. One of the two homologous polysaccharides isolated from *A. montona* cell culture showed a pronounced enhancement of phagocytosis *in vitro*. Arabino-3, 6-galactin protein displayed a strong anti-complementary effect and stimulated macrophages [48] to excrete the Tumor Necrosis Factor (TNF-alpha).

***Astragalus mongholics* Bunde (Fabaceae):** Galactoarabinan obtained from *A. mongholicus* has been demonstrated to stimulate phagocytosis, T lymphocytes and increase plasma cell counts.

***Asparagus racemosus* Wild (Lilliaceae):** *A. racemosus* protected rats against coecal-ligation induced sepsis and mice against *E. coli* peritonitis. Plant extract administration reduced the mortality rate due to *S. aureus* sepsis in neutropenic and hemisplenectomized mice. This plant extract reduced *C. albicans* induced sepsis and mortality. It is reported to have immunorestorative effect against the mylosuppression induced by single or multiple doses of cyclophosphamide [49].

***Azadirachta indica Juss* (Meliaceae):** Various preparation of *A. indica*, an evergreen tropical tree is used in Ayurveda and other systems of traditional medicine for the treatment of inflammatory disorders [50-54]. Fujiwara et al. [54] have described polysaccharides isolated from the bark of this plant to possess anti-tumor interferon inducing and anti-inflammatory activities. Aqueous extract of the bark has been shown to increase the production of Migration Inhibitory Factors (MIF) [55]. It inhibits complement activation by both Classical Pathway (CP) and Alternative Pathway (AP). Luminal dependent chemiluminescence activated human Polymorph nuclear leucocytes was also inhibited by this plant extracts [56,57].

Isolate (NB-11) from this plant has also been shown to enhance the induction of Delayed Type Hypersensitivity (DTH) response and antibody formation in mice [58]. Phenolic compounds contribute to the *in vitro* anti-inflammatory activity of its preparations [50,59].

***Boerhaavia diffusa* Linn:** Belongs to the family Nyctaginaceae. Roots of *B. diffusa* are documented in literature to possess diuretic properties and are useful in Jaundice, ascities, internal inflammations and gonorrhea. It is very good expectorant and is used for antistress activity [60]. The drug is reported to be useful for the eyes, dropsical swellings, heart diseases, blood purifier and maintains balance between vata, kapha. Its usefulness during enlargement of spleen and dyspepsia is also documented. It is in combating of scorpion string. The plant shows hepato-protective anti-inflammatory and cardiovascular activity. The leaves possess antitumor, appetiser, alexiteric activities, used in rheumatism and muscular pain, blood purifier and hasten delivery.

***Boswellia serrata* Roxb (Burseraceae):** The Alcoholic Extract of Salai Guggal (AESG), the oleogum resin of *Boswellia serrata*, has been shown to possess prominent anti-inflammatory and anti-arithritic activities [61]. Reduction of humoral antibody and development of DTH reaction to SRBC by AESG and Boswellic acids has been reported by [62]. It inhibits migration of leucocytes into the pleural cavity and reduced the volume pleural exudates. Antichemotactic activity has been demonstrated by its inhibitory effect on arthus reaction [62] and synthesis of catalysed mediator [63]. Salai guggal and boswellic acid have been shown to inhibit the proliferation of murine spleenocytes and thymocytes in response to mitogens [64].

***Cryptolepis buchanani* Roem and chult (Asclepiadaceae):** *Cryptolepis buchanani* Roem and Achult. Belongs to family Asclepiadaceae and famous sariva group. It holds a very prestigious position in Ayurveda. It is distributed throughout India, preferably in hot deciduous forests. The plant is used in traditional medicine as decoction given to children to cure them of rickets. It is also given to women in combination with Euphorbia microphylla Heyne, when lactation is deficient or fails. Different parts of this plant are used in sores, ascites, dropsy, anasarca, cholera, dysentery, body ache and snake bite. Roots of *C. buchanani* are used as a blood purifier. Ethanolic extract of roots and stem shows hypotensive and as central nervous system depressant and antihistaminic [65]. Paste given internally in abdominal pain [66].

Ethanolic extract of arial parts of plant shows diuretic activity [67]. Pounded roots are given to women to increase milk secretion [68]. Root bark is used in rheumatic pains [69]. Stem constituents are alkaloids and triterpenes, leaves constituents are A and B-amyrin and cryptolepine-the methylquinoline alkaloid of *Cryptolepis sanguinolenta* [70].

The alcoholic extract of the root shows the presence of sterols, reducing sugars and traces of glycosides exhibited antiplatelet effects *in vitro* in human, rabbits and rats. In rats, it exhibited ADP-aggregation *in vitro* with delayed on set and prolonged action *in vitro* cryptolepine disaggregated platelets aggregated by ADP, AA and thrombin. In addition, it exhibited an indirect fibrinolytic action in the rat possibly by causing the release of plasminogen activators from the vascular endothelium [71].

***Carthamus tinctorium* L (Compositae):** A water soluble polysaccharide isolated from blossoms of *Carthamus tinctorium* has been shown to induce antibody synthesis in mice following intraperitoneal injection [72].

***Carthamus ipecacuanha* (Brot) Rich (Rubiaceae):** Emetine an alkaloid isolated from *C. ipecacuanha* as an amoebicide and expectorant only has been demonstrated to possess antiviral activity [73]. Increased phagocytosis suggested an immunostimulatory action of emetine has been demonstrated by Wagner et al. [35].

***Curculigo orchioides* Gaerth (Lillaceae):** Curculigo side, isolated from *C. orchioides* has been reported to increase phagocytosis [74].

***Cynanchum caudatum* (Ascleplad aceae):** Cynaroside, a glycoside isolated from the roots of *C. caudatum* is also an immunostimulant as it has been shown to increase phagocytosis and cellular immunity in mice.

***Curcuma longa* L (Zingiberaceae):** *Curcuma longa* has been reported to possess anti-bacterial [75] anti-inflammatory, anti-arithritic [76-79] and anti-asthmatic properties [80]. Curcumin, the active ingredient in *C. longa* has shown anti-arithritic [81], cytotoxic and anti-tumor activities [82]. Curcumin has shown to inhibit mitogen induced proliferation of mouse splenocytes [64].

***Cryptolepis sanguinolenta* (Asclepiadaceae):** The alcoholic extract of the root shows the presence of sterols, reducing sugars and traces of glycosides exhibited antiplatelet effects *in vitro* in human, rabbits and rats. In rats, it exhibited ADP-aggregation *in vitro* with delayed on set and prolonged action *in vitro* cryptolepine disaggregated platelets aggregated by ADP, Anti-diarrhoel activity of *Cryptolepis sanguinolenta* was studied by Alexandra [83].

Cryptolepine is the main alkaloid of *Cryptolepis sanguinolenta* (Lindl.) Schlechter, a plant frequently used in West Africa, Ethanol and aqueous extract of roots were effective for 65 strains of Campylobacter jejuni, 41 strains of *Campylobacter coli* isolated from sporadic cases of gastroenteritis in Portugal and 86 strains of *Vibrio cholerae*, its activity was claimed to be equal to ampicillin. The results suggest that these roots could be a therapeutic alternative for bacterial etiologic diarrhea in West Africa. Studies were conducted on inhibition of Carrageenan induced oedema by Cryptolepine [83,84]. The roots of *Cryptolepis sanguinolenta* (Lindl.) Schlechter (Asclepiadaceae) acts as anti-hepatitis and bronchodilatory [85-87].

***Dionaea muscipula* E (Droseraceae):** Out of four napthoquinones droserone, 3-chloroplumbagin, plumbagin and hydroplumbagin-4-0-B- glucoside isolated from the plant plumbagin has been shown to increase the phagocytosis of human granulocytes *in vitro*. Hydroplumbagin glucoside has been shown to enhance the proliferation of T-lymphocytes.

***Epimedium davidii Franch* (Berberidaceae)**

A novel flavonoid compound baohuoside-1 (3,5,7-trihydroxy-4-methoxyl-8- prenylflavone-3-0-a- L- rhamnopyranoside) isolated from the plant has been shown to produce significant suppressive effect on neutrophil chemotaxis, mitogen-induced lymphocytes transformation, mixed lymphocyte culture, NK- cell cytotoxicity and IL-2 production [88]. These inhibitory effects suggest anti-inflammatory/immunosuppressive potential of baohuoside - 1.

***Eucommia ulmoides* Oliver (Eucommiaceae)**

An acid polysaccharide eucomman isolated from the dried bark of *E. ulmoides* has shown significant potentiation of reticuloendothelial system using carbon clearance test in mice [89].

***Eupotorium cannabinum* L. (Asteraceae):** *Eupotorium cannabinum* is currently used as an ingredient of immunostimulatory drug preparation. Of the two homogeneous polysaccharides (PI and PII) isolated from *E. cannabinum* and *E. perfoliatum*, PI has been reported to differntiately to enhance the microphagocytosis chemiluminescence by a much larger margin than PII [90].

***Gynostemma pentaphyllum* (Cucurbitaceae)**

Total saponins of *G. pentaphylla* markedly acted against the immunity inhibition due to cyclophosphamide administration in experimental animals. Saponins have shown to have immunomodulatory action in healthy mice.

Hemidesmus indicus (Linn.) R.Br belongs to family Asclepiadaceae.

The roots of this plant are used as a substitute for sarsaparilla. It is considered to be demulcent alternative, diaphoretic, diuretic and tonic. Root is bitter and is used in loss of appetite, fever, skin diseases, leucorrhoea, syphilis, rheumatism, scorpion sting and snake bite. It is also used as aphrodisiac, antipyretic, cure for leprosy, leucoderma, itching, good for the diseases of the brain, liver and kidney. The plant is considered useful in fever [91]. It is useful in leucoderma, paralysis and epileptic fits in children [60]. The aqueous extract caused a slight increase in the urinary flow in rats. Rise in B.P. was observed with alcoholic extract in rats.

The petroleum ether, chloroform and alcoholic extracts of *H. indicus* roots showed antibacterial activity. Essential oil obtained from the plant exhibited marked antibacterial activity against *B. proteus*, PS, aeruginosa, staph, pyogenes and *E. coli* at a concentration of 0.2% [92]. The aqueous, ethanolic extract of *H. indicus* showed antiviral activity (100%) against Ranikhet Disease Virus (RDV) [93]. Ethyl acetate and saponin from *H. indicus* was found to have anti-inflammatory activity against formaline induced oedema [94]. The survey revealed that twenty one plant species are used by tribals of Kerala for treating cancer symptoms. The plants include *Hemidesmus indicus* [95]. *H. indicus* popularly known as Indian Sarsaparilla finds extensive application in the Indian system of medicine as blood purifier and anti-rheumatic agents.

Two new coumarin-lignoids: - *Hemidesmin–1, Hemidesmin–2,* have been isolated from the root of *H. indicus*. A 95% ethanolic extract of *H. indicus* has been reported to suppress the Cell Mediated (CMI) and humoral components of immunity [38]. Mice, infected with *M. leprae*, when treated with *Hemidesmus indicus* showed a delay in multiplication of organisms in the mouse foot pads while supporting the anti-leprotic action of an extract on *Anantamul* (*H. indicus*) [96].

***Holarrhena antidysenterica* (Linn.) Wall:** It belongs to family Apocynaceae. It is found throughout India, and is safe cheap reliable

drug for the treatment of diarrhea, spleenic disorders, cholera, menorhagia and dog bites [97]. The bark is used as anti-helminthic, in skin diseases, fever, piles, leprosy, kapha, thirst and dysentery. Leaves of *H. antidysenterica* are used as tonics, aphrodisiac, muscular pain, in chronic bronchitis and for cure of boils and ulcers. It is useful in regulating the menstruation. Seeds are used for fatigue, as hepatoprotective, used in leprosy, hallucinations and astringent to the bowels. Seed oil of *H. antidysenterica* showed antifungal action [60,98,99]. The therapeutic utility of kurchi in acute and chronic amoebic dysentery has been known for a long time [99,100].

H. antidysenterica showed promising activity against experimental amoebiasis in rats and hamster [75,101]. It lowers the B.P. in dogs [102]. Studied the antiviral activity of bark extract (50% ethanolic) against Potato Virus X (PVX). The fruit Extract (50% ethanolic) showed antiprotozoal effect against *E. histolytica* stain STA, Trypanosoma evansi. Dhar et al. [103] has demonstrated anticancer effect against human epidermoid carcinoma of the nasopharynx in tissue culture and hypoglycemic activity in rats. *H. antidysenterica* (95% ethanolic extract) has been found to enhance the phagocytic functions of Reticulo-Endothelial System (RES) and suppress the humoral component of the immune system [38].

***Ichnocarpus frutescens*:** R.Br.Sy. (Linn.) Belongs to family Apocynaceae. It is found in all parts of India. Roots are used as a demulcent, alternative tonic, diuretic, diaphoretic and as a substitute for Indian Sarsaparilla. Leaves and stems are used in fever, roots used in skin diseases, useful in night blindness, bleeding of gums, ulcerated tongue, sores, enlargement of spleen, convulsions, haematuria, dysentery cough, dog bite, in snake bite and atrophy [97,104]. The ethanolic extract (50%) of *I. frutescens* (Whole plant) showed anti-viral activity against ranikhet disease virus but was inactive against Vaccinia virus. It had anti-bacterial, anti-fungal, anti-protozoal, anti-helminthes, hypoglycemic and anti-cancer activity [105]. Alkaloids and flavinoids were found in roots [106]. It has no effect on respiration and blood pressure in cats and dogs [103].

***Malva verticellata* L. (Malvaceae):** A novel acidic polysaccharide designated as MVS-VI isolated from seeds of *M. verticellata* has been shown [107] to possess significant potentiating activity on reticulo-endothelial system using carbon clearance test and anti-complementary activity.

***Mesua ferrea* L.(Clustaceae):** Bhide et al. [108] have reported the anti-anaphylactic activities of the seed oil of *Mesua ferrea.*

***Ocimum gratissimum* L. (Labiatae):** A 95% ethanolic extract of *O. gratissimum* leaves have been reported [38] to improve the phagocytic function of reticulo-endothelial system without affecting the humoral or cell mediated immune responses in mice.

***Ocimum sanctum* L. (Labiatae):** Godhwani and associates have reported the immunostimulant properties of 50% methanol extract and aqueous suspensions of *O. sanctum*. Both methanol extract and aqueous suspension of *O. sanctum* leaves have been found to enhance the humoral responses to SRBC and typhoid 'H' antigens and to increase the count of Erosetting lumphocytes.

***Panax ginseng* Meyer (Araliaceae):** *Panax ginseng* has been classified as an adaptogenic or anti-stress drug plant [109]. In combination with 6-MFA (an interferon inducing antiviral substance of viral origin), has been found to significantly enhance antibody titre against SRBC. Cell mediated immunity Semliki Forest Virus antigen, natural killer cell activity in mice and production of interferon by an interferon inducer 6-MFA has been observed to be effected. This plant augments natural killer cells and antibody dependent cytotoxic activities and increase the protective effect against above described antigen as compared to 6-MFA along [110].

Polysaccharides from ginseng root were found to markedly stimulate phagocytosis and production of antibody [111]. They caused an increase of serum complement content in guinea pigs, raised serum IgG level in mice and increased B-lymphocytes to T-lymphocyte cell ratio. The polysaccharide fractions from hot water extract of *P. ginseng* have been found to have immunological, antitumor and hypoglycemic activity [112].

Administration of ginseng polysaccharides (400 g/kg to 800 g/kg) for 10 days markedly increased the number of Plaque Forming Cells (PFC) and specific rosette forming cells in tumor bearing mice immunized with SRBC [113]. The two polysaccharides have the similar effect on immune functions causing increase in weight of spleen, enhanced phagocytosis, promoting the production of serum specific antibody hemolysin and IgG level in mice [114]. Enhanced DTH of foot pad induced by SRBC is also controlled by above mentioned isolate.

***Picrorhiza kurroa* Royle ex. Benth. (Scrophulariaceae):** Root extracts of the small Himalayan herb *Picrorhiza kurroa* are used therapeutically in traditional medicine of almost of all Asian countries to treat many conditions of illness including inflammatory disorders [5,115]. *P. kurroa* extract is being used in the treatment of bronchial asthma [116], infectious hepatitis [117], and joint pain [118] has been documented. 95% ethanolic extract of roots and leaves have been shown to enhance the cell mediated and humoral immune responses to sheep erythrocytes and phagocytic function of reticuloendothelial system [38,62]. *P. kurroa* was also found effective in vitiligo patients [119]. A glycoside fraction from *P. kurroa* roots has been shown to augment the bronchodilatory effect of isoprenaline adrenaline, rendering guinea pigs less sensitive to histamine. It reduces histamine contents of lung tissues and inhibit immunological release of histamine and show reacting substance of anaphylaxis (SRS-A) from chopped lungs [120]. Iridoid glycosides Picroside-I and kutkoside have been found to stimulate the cell mediated and humoral components of immune system, improve the phagocytic function of RES and abrogate the suppressive effects of Cyclophosphamide and betamethasone [121].

***Plumeria acutifolia*:** Linn.R.Br. Belongs to the family Apocynaceae: It is an evergreen partly deciduous tree, cultivated as an ornamental plant throughout India. Root bark has been used as purgative, in gonorrhea and venereal sores. Stem bark is given in diarrhea. Latex of this plant is employed as a rubefacient in rheumatism. Jain and Tarafder [97] described its use in indigestion and cholera. Flowers are potent contraceptives [122]. Chak and Patnaik [123] demonstrated local anesthetic activity of aqueous extract of *P. acutifolia* in rabbits, guinea pigs, cats and dogs. Antibacterial/antifungal activity has been reported by [124]. Root bark cures tumors and rheumatic pains. Plasters made of the bark are said to be useful in dispersing hard tumors [60]. Plumeride isolated from *P. acutifolia* has been reported to possess anti-fungal [125] and immunostimulatory effect in mice, on cell mediated and humoral responses. Triterpenes from leaves of *P. acutifolia* have shown strong anti-tumor activity. Bark extract possess stimulant action and is powerful anti-therapeutic [126].

***Remannia glutinosa* Livosch Var. hueichingensis (Scrophulariaceae):** On immunological investigations two new phenethyl alcohol glycosides designated as Jionoside A1 and B1 have been shown to possess immunosuppressant activity suppressing Haemolytic Plaque Forming Cells (HPFC) in mice [127].

***Sida* spp. (Malvaceae):** Dixit et al. [40] have reported *S. cardifolia* L., *S. rhombifolia* L. and *S. veronicaefolia* Lamk to increase humoral antibody response to *S. typhimurium* 'O' antigen and to increase the survival time of rabbits against virulent *Staphylococcus aureus* challenge. However, no direct antibacterial activity against *S. aureus* or specific change in immunoglobulin pattern on treated animals has been recorded.

***Sphaeranthus indicus* L. (Compositae):** A new sesquiterpene glycoside, Parthenolide isolated from the flowers of *S. indicus* has been shown to produce 40% increase in the antibody secreted cells. It has been used for glandular swelling, bronchitis, jaundice and nerves depression [128].

***Strobilanthes hyneanus* Nees (Acanthaceae):** The aqueous and 95% ethanolic extract of stem have been shown to possess analgesic, anti-inflammatory and immuno-suppressive activity. In mice treated with these extracts, significant suppression of antibody formation against sheep red blood cells was noticed comparable to betamethasone. It affects neurologic disorders oedema, healing of ulcers.

***Swertia chirata* Ham:** Belongs to family Gentianceae: It is used as tonic, anti-helminthic, anti-diarrhoeal. It is laxative, used in fever gout, ulcers and acts as anti-inflammatory [129], cures burning sensation, pain in body, asthma, bronchitis and is good in vomiting. It is used as an anti-worm [60]. Hexane fraction of *S. chirata* induces fall in blood sugar after single oral administration in albino rats. A multiple dose of *S. chirata* has significantly lowered the blood sugar while showing an increase in plasma IRI along with a significant rise in Liver glycogen. Swerchirin may have application in control of diabetes mellitus [105].

***Taraxacum platycarpum* (Compositae):** A polysaccharide fraction from *T. platycarpum* has been shown to possess a potent immune-potentiating activity with a antitumor activity [130].The fraction having small amount of protein inhibited the growth of solid tumor and increased the peritoneal exudates cells and immune-organ weight in normal mice and hypersensitivity in tumor bearing mice.

***Tinospora cordifolia* Miers (Menispermaceae):** The ethanolic extract of *T. cadiofolia* has been reported to enhance the cell mediated immunity and non-specific resistance in mice [38]. It is associated with early wound healing in patients with perforated peritonitis and local sepsis.

Dahanukar [49] have reported *T. cardifolia* to protect rats against coecal ligation induced abdominal sepsis and mice against *E. coli* peritonitis. The plant induced leucocytosis with predominant neutrophilia associated with stimulation of phagocytic and bactericidal capacity of neutrophils and macrophages. Rege and associates have reported the restorative effect of aqueous extract of *T. cardifolia*.

***Tripterygium wilfordii* Hook. F. (Celastraceae):** Wilfortrine and euonine isolated from *T. wilfordii* showed marked depressant effects on humoral and cell mediated immunity. Wilfortrine exhibited depressant effect on graft vs. host reaction and marked suppressant effects on DTH reaction in mice. Wilfortrine and euonine significantly decreased the clearance rate of charcoal particles and weights of spleen and thymus [131].

***Tylophora indica* Burm F. Merr. (Asclepiadaceae):** The ethanolic extract (95%) of *Tylophora* leaves has been shown to possess immunosuppressive activity [38]. At 100 mg/kg P.O. dosage, it significantly inhibited the expression of SRBC induced DTH reaction and humoral antibody synthesis, reduced the carbon clearance rate and prolonged the graft rejection time. Sharma et al. [64] have shown tylophorine to significantly reduce the proliferative responsiveness of splenocytes to PHA, Con- A, and LPS at a concentration of 125 ug/ml. It has been used against bronchial asthma [5] and rheumatism [3] and anti-asthematic effect [132,133].

***Uncaria tomentosa* DC prod. (Rubiaceae):** Pure oxindole isolated from *U. tomentosa* has been reported to increase phagocytosis suggesting its immunostimulatory activity [134].

***Viscum album* L. (Loranthaceae):** Immunomodulating properties have been attributed to polysaccharide fraction. It has a biphasic effect on mononuclear phagocytic system and an adjuvant effect on humoral immune response [135]. It has no effect on human granulocyte phagocytosis *in vitro* [30].

***Woodfordia fruticosa* Kurtz. (Lythraceae):** A macerate of flowers of *Woodfordia fruticosa* has been shown to inhibit both the alternative and classical pathways of human complement system, and zymosen induced chemiluminescence of human PMNL and proliferation of T-cells [136].

***Zexmenia brevifolia* A Gray (Compositae):** *Zexbrevins* A and B, the two germ macrolides isolated from *Zexmenia brevifolia* have been shown to display a pronounced activity as immuno adjuvants. Administration of *zexbrevin* prior to or along with antigen (SRBC, BSA or mouse albumin) has been observed to produce a pronounced increase in the number of specific rosette like cells in the mouse spleen. It has been shown to have no mitogenic activity.

Literature cited so far put forth the claim that natural products represent prominent and promising sources of molecules with interesting immunomodulating properties. This line of research although is a programmed way is relatively young, but fast growing, Advancement in the field of immuno-pharmacology, plant products have been reviewed by Lindequist and Teuscher [2,47,137].

Leads derived from traditional medicine through scientific studies appear to be influential for the discovery of immunomodulatory compounds and novel mechanisms of action. Such compounds may serve innovative to drug development, and can be of great impact on drug therapy as a whole. The brief review of the immune-pharmacological work done on medicinal plants in the past brings out potential of these herbals for effectively modulating the immune expression of an individual and opens a great avenue of researchers.

Although terms depicting immune-stimulation and immune-suppression are not exactly described in the ancient literature but the therapeutic efficacy described points more or less towards their use as immunomodulators. Recently many plants have been screened on the basis of their use as antibacterial, anti-inflammatory, anti-viral, anti-stress, anti-fungal and antitumor activities. These plants/extracts or isolates are good candidates for modern immunological test screening. Few of plants documented in literature and listed below were subjected to a battery of preliminary tests for assessing their activity as corrections of immune system.

We have described some medicinal plants along with their botanical name, common name, part used, chemical constituent and their biological activities with references (Table 1).

Author Contributions

All authors contributed equally to this work. Amit Kumar was involved in developing the idea and designing of the manuscript. Govind Yadav analyzed the data. Amit Kumar prepared the original draft. Amit Kumar and Govind Yadav reviewed and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

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Table 1: A brief description of common plant-derived immunomodulators.

Botanical name (Family)	Common name	Part used	Chemical constituents	Biological activities with reference
Ocimum sanctum Linn. (Labiateae)	Tulasi	Entire plant	Essential oils such as eugenol, cavacrol, derivatives of ursolic acid, apigenin	Carminative, stomachic, antispasmodic, antiasthmatic, hepatoprotective [138]
Morus alba Linn. (Moraceae)	Brahmdaru	Fruits, leaves, bark	Flavonoids, anthocyanins	Expectorant, ypocholesterolaemic, Diuretic [139].
Panax ginseng Wall. (Araliaceae)	Ninjin	Fruits, root	Saponins such as ginsenosides,panaxdiol, panaxtriole and oleanolic acid	Adaptogenic properties, Antiarrhythmic [140],[141]
Achillea millefolium C. Koch (Compositae)	Yarrow	Leaves	Flavonoids, alkaloids, polyacetylenes, coumarins, triterpenes	Anti-inflammatory, antispasmodic, antipyretic, diuretic [142].
Aloe vera Tourn. ex Linn. (Liliaceae)	Kumaari	Gel from leaves	Anthraquinone glycosides	Purgative, emmenagogue, emollient, antinflammatory [140,143].
Andrographis paniculata Nees (Acanthaceae)	Kaalmegha	Leaves	Diterpenes	Hepatoprotective, antispasmodic, blood purifier, febrifuge. [140,144]
Asparagus racemosus Wild. (Liliaceae)	Shatavaari	Roots	Saponins, sitosterols	Ulcer healing agent, nervine tonic, antigout [145,146],
Murraya koenigii (L) Spreng. (Rutaceae)	Surabhini-nimba	Leaves	Coumarin, carbazole alkaloids, glucoside	Antifungal, insecticidal, insecticidal [140,147]
Couroupita guianensis Aubl. (Lecythidaceae)	Nagalinga	Fruits, flowers	Steroids, flavonoids, phenolics	Antifungal [148].
Tinospora cordifolia Miers. (Menispermiaceae)	Amrita, guduuchii	Entire herb	Alkaloidal constituents such as berberine, tinosporic acid	Hypoglycaemic agent, antipyretic [145,149].
Lagenaria siceraria Mol. (Cucurbitaceae)	Katu-tumbi	Leaves, fruit	Cucurbitacin, beta-glycosidase	Purgative, emetic [150].
Terminalia arjuna Roxb. (Combretaceae)	Arjuna	Leaves, bark	Flavonoids, oligomeric	Cardiotonic, diuretic, prescribed for Hypertension [151].
Bauhinia variegata Linn. (Caesalpiniaceae)	Kaanchana	Roots, bark, buds	Flavonoids, beta-sitosterol, lupeol	Antifungal, astringent [152].
Urena lobata Linn. (Malvaceae)	Naagabala	Roots, flowers	Flavanoids	Diuretic, emollient, antispasmodic [153].
Gymnema sylvestre R.Br. (Asclepiadaceae)	Gurmaar	Leaves	Sapogenins	Antidiabetic, diuretic, antibilious [154].
Cordia superba Cham. and C. rufescens A. DC. (Boraginaceae)	Shleshmaataka	Leaf, fruit, bark	Alpha-amyrin	Anti-inflammatory, antimicrobial [155].
Picrorhiza scrophulariiflora Benth. (Scrophulariaceae)	Kutki	Roots	Iridoid glycosides, amphicoside	Antioxidant [156].
Heracleum persicum Desf. (Apiaceae)	Golpar	Shurb	Flavonoids, furanocoumarins	Antimicrobial [157].
Cissampelos pareira Linn. (Menispermiaceae)	Paatha	Roots	Hayatine alkaloids	Antipyretic, analgesic, antilithic [158].
Abutilon indicum linn. (Malvaceae)	Atibalaa	Whole plant	Flavonoids, triterpenoids	Diuretic, antibacterial [159].
Chlorophytum borivilianum Sant. F (Liliaceae)	Safed musli	Roots	Sapogenins	Antifungal [160]
Alternanthera tenella Colla (Amaranthaceae)	Snow Ball	Herb	Flavonoids, triterpenes	Antitumor, anti-inflammatory [161]
Ganoderma lucidum (Fr.) P. Karst. (Polyporaceae)	Reishi mushroom	Whole plant	Flavonoids, triterpenes	Antioxidant [162].
Nyctanthes arbor-tristis L. (Oleaceae)	Paarijaata	Leaf, seeds	Iridoid glucosides	Anti-inflammatory, antispasmodic [163].
Actinidia macrosperma C. F. Liang (Actinidiaceae)	Actinidia	Fruits	Alkaloids, saponins	Antileprotic [164].
Acacia catechu Willd. (Leguminosae)	Khadira	Leaf	Flavonoids, quercetin	Hypoglycaemic, astringent [145,165].
Boswellia spp. (Burseraceae)	Shallaki	Gum resin	Triterpenes, ursanes	Hypoglycaemic [166]
Hibiscus rosa- sinensis Linn. (Malvaceae)	Japaa	Flowers	Cyclopropanoids	Antidiarrheal, anti-inflammatory [167].
Cleome gynandra Linn. (Capperdiceae)	Tilaparni	Leaf, seeds, rots	Hexacosanol, kaempferol	Anti-inflammatory [167].
Hyptis suaveolens (L.) Poit. (Lamaceae)	Tumbaaka	Leaf, flowers	Lupeol, beta-sitosterol	Carminative, antispasmodic [168].
Randia dumetorum Lamk. (Rubiaceae)	Madana	Fruits	Saponins, triterpenes	Chlorosis, antiarthritic [169].

Allium hirtifolium Boiss. (Alliaceae)	Persian shallot	Herb	Thiosulfinates, flavonoids	Antirheumatic, anti-inflammatory [170]
Citrus natsudaidai Hayata (Rutaceae)	Japanese summer grape fruit	Fruit	Auraptene, flavonoids	Antioxidant [171]
Acanthopanax sessiliflorus (Rupr. & Maxim.) (Araliaceae)	Prickly spine	Shoots and roots	Biopolymers	Lympho-proliferative activity [172].
Agelas mauritianus (Porifera)	Agelas	Sponge	Glycolipid (a-galactosylceramide)	Phagocytotic activity [173].
Aphanothece halophytica (Chroococcales)		Cyanobacterium	Exopolysaccharide	inhibits influenza virus [174].
Apium graveolens Linn. (Apiaceae)	Celery Seeds	Leaves, seeds	Flavonoids, coumarins	Anti-inflammatory [175]
Genus Ardisia (Myrsinaceae)	Marlberry	Shrub, Branches and leaves	Peptides, saponins, Isocoumarins, quinones and alkyl phenols	Antimetastatic drug, anti-HIV property [176]
Genus Aristolochia (Aristolochiaceae)	Pipevine	Leaves	Aristolochic acid	Antiangiogenic, employed in prostate cancer [177]
Artemisia annua Linn. (Compositea)	Wormwood	Herb	Artemisinin	Immunosuppressive [178]
Genus Aspergillus (Trichocomaceae)	Aspergillus	Fungus	Polyene, triazole	Antifungals [179]
Botryllus schlosseri (Botryllidae)	Botryllus	Tunicates	Cytokines	Antioxidant, antiviral, antimicrobial and antitumoral [180].
Bidens pilosa L. (Asteraceae)	Beggar-ticks	Flowers, leaves	Polyacetylenes	Anti-inflammatory, immunosuppressive, antibacterial and antimalarial [181].
Boerhaavia diffusa (Nyctaginaceae)	Punarnava	Herb	Alkaloid	Immunostimulatory [182].
Bugula neritina L. (Bugulidae)	Brown bryozoans	Marine invertebrates	Macrocyclic lactones	Immunomodulator [183].
Byrsonima crassa Nied. (Malpighiaceae)	Byrsonima	Leaves	Flavonoids, tannins, terpenes	Antimicrobial, antioxidant [184].
Calendula Officinalis L. (Asteraceae)	Garden Marigold	Flowers	Polysaccharides, proteins, fatty acids, carotenoids, flavonoids, triterpenoids	Antitumor antiviral activity, anti-HIV properties [185].
Camellia sinensis L. (Theaceae)	Tea	Leaves	Epigallocatechin gallate, quercetin, gallicacid	Anticancer activity, lipid lowering activity, anticataract activity, hepatoprotective and Antioxidant [186]
Cannabis sativa (Cannabaceae)	Common hemp	Leaves	Cannabinoids	Immunomodulatory [187].
Carpobrotus edulis L. (Aizoaceae)	Fig Marigold	Flowers, fruit	Alkaloids	Immunomodulator [188].
Centella asiatica Linn. (Umbelliferae),	Brahmi	Herb	Triterpenoid saponins	Immunomodulator [189].
Cistanche deserticola (Orobanchaceae)	Cistanche	Herb	Polysaccharide	Immunomodulator, mitogenic and comitogenic activities [190].
Cliona celata (Clionaidae)	Borimg sponge	Sponge	Clionamide, dehydrodopamine	Antibacterial activity [191].
Cordyceps militaris L. (Clavicipitaceae)	Militaris	Fungus	Cordycepin, cordyceps acid	Anti-inflammatory [192].
Crinum latifolium Andr. (Amaryllidaceae)	Milk and Wine Lily	Herb	Alkaloids	Mmunomodulator [193].
Dracocephalum Kotschyi (Lamiaceae)	Dragon-Head	Herb	Essential oil	Immunomodulator [194].
Echinacea angustifolia (Asteraceae)	Cone flower	Flowers	Polysaccharide	Treatment for common cold, Immunomodulator [195].
Eclipta alba L. (Compositae)	Bringraja	Leaves	Triterpenoid glucoside	Anticancer, antileprotic, analgesic, antioxidant, antimyotoxic [196].
Euphorbia hirta linn. (Euphorbiaceae)	Asthma weed	Herb	Quercitol, myricitrin, gallic acid	Anti-inflammatory activity, sedative and anxiolytic activity [197].
Evolvulus alsinoides Linn. (Convolvulaceae	Shankhpushpi	Herb	Alkaloids	Brain tonic [198].
Haussknechtia elymatica (Apioideae)	Haussknechtia	Herb	Phenolics	Immunomodulator [199].
Inonotus obliquus Pers. (Hymenochaetaceae)	Chaga Mushroom	Mushroom	Polysaccharide	Antitumor [200]
Larrea divaricata DC. (Zygophyllaceae)	Creosote Bush	Herb	Lignans	Anti-inflammatory [201].
Lycium barbarum Linn. (Solanaceae)		Fruits	Polysaccharide-protein complexes	Antioxidant [202].
Matricaria chamomilla (Rhabdoviridae)	Chamomile	Flowers	Protein	Mmunomodulator [203].
Mollugo verticillata L. (Molluginaceae)	Carpetweed	Herb	Quercetin, triterpenoid glycosides	Immunomodulator [204].
Moringa oleifera L. (Moringaceae)	Sahijan	Leaves	Vitamin A, B, C, carotenoids, saponins	Antioxidant [205].

Pestalotiopsis leucothes (Amphisphaeriaceae)		Fungus	Terpenes	Immunomodulator [206].
Piper longum L. (Piperaceae)	Pipali	Fruits	Alkaloids	Antioxidant [207].
Rhodiola imbricate Gray. (Crassulaceae)	Roseroot	Rhizomes	Phenolics	Immunostimulating properties [208].
Silybum marianum L. (Asteraceae)	Milk Thistle	Flowers	Flavonoid	Antioxidant [209].
Salicornia herbacea (Chenopodiaceae)	Glasswort	Herb	Polysaccharides	Immunomodulator [210].
Viscum album L. (Loranthaceae)	Mistletoe	Leaves and young twigs, berries	Viscotoxins, polyphenols, polysaccharides	Antitumoral effect ooong [211].
Thuja occidentalis L. (Arborvitae)	White cedar	Leaves	Polysaccharides	Immunomodulator.

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