Review Article

Natural Immunomodulators: Promising Therapy for Disease Management

Muskan Altaf Tamboli, Rutuja Ramdas Bhosale, Naziya Ashpak Tamboli

From, Professor & Amp, Department of Pharmacology, Sahydri College of Pharmacy, Methwade, Maharashtra, India

ABSTRACT

The immune system comprises a complex group of processes that provide defense against diverse pathogens. These defenses can be divided into innate and adaptive immunity, in which specific immune components converge to limit infections. We reviewed currently available experimental and clinical evidence to prove the efficiency, safety, and feasibility of immunomodulation *in-vitro* and *in-vivo*. We also reviewed the advantages and limitations of the described techniques. Despite its limitations, immunomodulation is considered as the therapy itself or as an adjunct with promising results and developing potential. Many plants and some phytoconstituents responsible for immunomodulation have been explained. The study also discusses biological screening methods for various plant drugs that focus on revealing the mechanism involved in immunomodulation. Nutraceuticals are essential food constituents that provide nutritional benefits as well as medicinal effects. The benefits of these foods are due to the presence of active compounds such as carotenoids, collagen hydrolysate, and dietary fibers.

Key words: Immune system, Immunomodulation, Nutraceutical plants, Anti-inflammatory

Nutraceuticals which have also been called medical foods, designer foods, phytochemicals, functional foods and nutritional supplements, include such everyday products as “bio” yoghurts and fortified breakfast cereals, as well as vitamins, herbal remedies, and even genetically modified foods and supplements. Nutraceuticals may be used to improve health, delay the aging process, prevent chronic diseases, increase life expectancy, or support the structure or function of the body [1]. Immunomodulation is an alteration of the immune system and interfering with its functions; if it results in an enhancement of immune reaction, it is named an immune stimulation which primarily implies stimulation of non-specific system, that is, granulocytes, macrophages, complement, certain T-lymphocytes and different effector substances. Immunosuppression implies mainly to reduce resistance against infections, and stress and may occur on account of environmental or chemotherapeutic factors. Immunostimulation and Immunosuppression both need to be tackled to regulate normal immunological functioning. Hence, both immunostimulating and immunosuppressing agents have their standing, and the search for better agents exerting these activities is becoming a field of major interest all over the world [2].

Many immunomodulators in clinical use are cytotoxic drugs with significant adverse effects. To overcome toxicity and existing available cytotoxic drugs there is a need for new immunomodulatory medications. Traditional medicines are the oldest approach for treating and managing any illness without causing severe or minor adverse effects. Further, the search for chemicals of plant origin as fresh lead for the creation of potent and safe immunomodulators is receiving a lot of attention [3].

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Correspondence to: Muskan Altaf Tamboli, Department of Pharmacology, Sahydri College of Pharmacy, Methwade, Maharashtra, India. **Email:** muskanatamboli17@gmail.com **Tel.:** +91 7387963031

IMMUNITY

The resistance offered by the host to the harmful effect of pathogenic microbial infection is called immunity [4].

Types of Immunity: Broadly speaking, immunity or body defense mechanism is divided into two types, each with humoral and cellular components [5].

Natural or innate immunity is ***non-specific*** and is considered the first line of defense without antigenic specificity. It has two major components: **a)** ***Humoral:*** comprised by complement. **b)** ***Cellular:*** consists of neutrophils, macrophages, and natural killer (NK) cells.

Specific or adaptive immunity is ***specific*** and is characterized by antigenic specificity. It too has two main components: **a)** ***Humoral:*** consisting of antibodies formed by B cells. **b)** ***Cellular:*** mediated by T cells.

The various components of both types of immunity are interdependent and interlinked for their function. The mechanisms of innate and adaptive immunity are demonstrated in (Figure 1) [6].

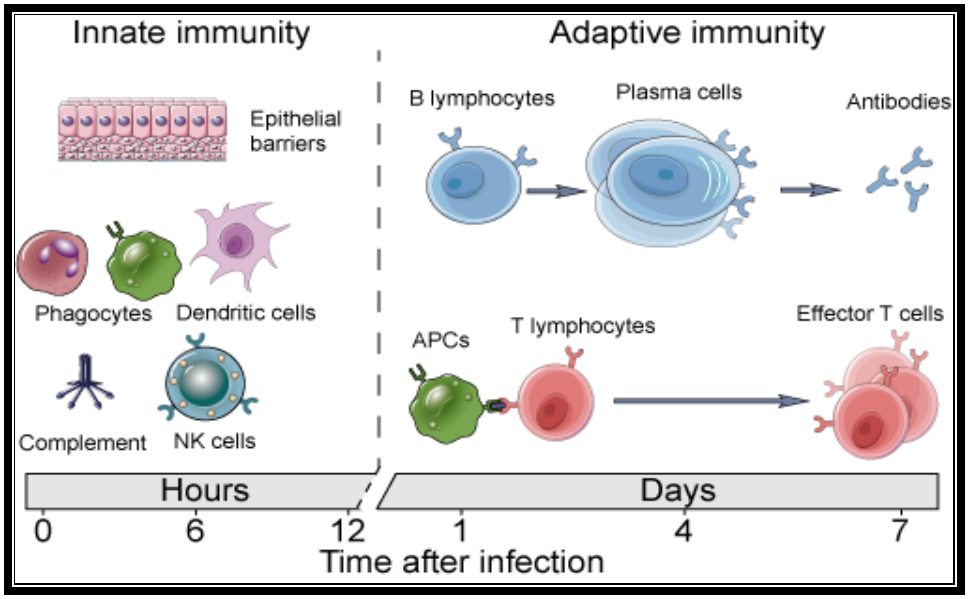

Figure 1 - Mechanism of Innate Immunity and Adaptive Immunity

Structure of Immune System [5]

Organs of Immune System: Although functioning as a system, the organs of the immune system are distributed at different places in the body. These are as under:

a) Primary lymphoid organs: i) Thymus ii) Bone marrow
b) Secondary lymphoid organs: i) Lymph nodes ii) Spleen iii) MALT (Mucosa-Associated Lymphoid Tissue) located in the respiratory tract and GIT.

Cells of Immune System [5]

The cells comprising the immune system are as follows:

Lymphocytes: Lymphocyte is the master of the human immune system. Morphologically, lymphocytes appear as a homogeneous group but functionally two major lymphocyte populations, *T and B lymphocytes* are identified; while a third type, *NK cells*, comprises a small percentage of circulating lymphocytes having the distinct appearance of large granular lymphocytes [5].

Monocytes and Macrophage: The role of macrophages in inflammation consists of circulating monocytes, organ-specific macrophages, and histiocytic. Circulating monocytes are immature macrophages and constitute about 5% of peripheral leucocytes. They remain in circulation for about 3 days before they enter tissues to become macrophages. The macrophage subpopulations like the dendritic cells found in the lymphoid tissue and Langerhans cells seen in the epidermis, are characterized by the presence of dendritic cytoplasmic processes and are active in the immune system [5].

Mast cells and Basophil: Basophils are a type of circulating granulocytes (0-1%) while mast cells are their counterparts seen in tissues, especially in connective tissue around blood

vessels and in submucosal locations. Basophils and mast cells have IgE surface receptors; thus, on coming in contact with antigen binding to IgE (e.g. allergic reaction to parasites), these cells get activated and release granules i.e. degranulate. These granules contain substances such as histamine platelet-activating factor, heparin, and certain chemical mediators (e.g. prostaglandins, leukotrienes). Mast cells and basophils are thus involved in mediating inflammation in allergic reactions and have a role in wound healing [5].

Neutrophils: Polymorphonuclear neutrophils (PMNs) are normally the most numerous of the circulating leucocytes (40-75%). The cytoplasm of PMNs contains lysosomal granules of three types: primary (azurophilic), secondary, and tertiary. PMNs have similar functions to those of macrophages and are therefore appropriately referred to as '*macrophages*' owing to their role as the first line of defense against an invading foreign organism in the body. However, these cells have limitations in size and type of organisms to be engulfed e.g. while they are capable of acting against bacteria and small foreign Particulate material but not against viruses and large particles [5].

Eosinophils: Eosinophils are also circulating granulocytes (1-6%). These cells play a role in allergic reactions and intestinal helminthiasis. The granules of eosinophils contain lysosomal enzymes, peroxidases, and chemical mediators of inflammation (e.g. prostaglandins, leukotrienes). On coming in contact with IgE opsonized antigen (e.g. helminths), eosinophils degranulate and release the chemicals stored in granules and incite inflammation [5].

Diseases of Immunity

The diseases of the immune system are broadly classified into the following four groups:

Immunodeficiency Disorder: Failure or deficiency of the immune system, which normally plays a protective role against infections, manifests in the occurrence of repeated infections in an individual having immunodeficiency disease. Traditionally, immunodeficiency diseases are classified into two types:

a. ***Primary immunodeficiencies*****:** are usually the result of genetic or developmental abnormality of the immune system.
b. ***Secondary immunodeficiencies:*** arise from acquired suppression of the immune system. Since the first description of primary immunodeficiency by Bruton in 1952, an increasing number of primary and secondary immunodeficiency syndromes have been added to the list, the latest addition being the acquired immunodeficiency syndrome (AIDS) in 1981 [5].

Hypersensitivity Reactions: Hypersensitivity is defined as an exaggerated or inappropriate state of normal immune response with the onset of adverse effects on the body. The lesions of hypersensitivity are a form of antigen-antibody reaction. These lesions are termed hypersensitivity reactions or immunologic tissue injury, of which 4 types I, II, III, and IV. Depending upon the *rapidity, duration, and type* of the immune response, these 4 types of hypersensitivity reactions are grouped into immediate and delayed types [5].

a. Immediate type in which on the administration of antigen, the reaction occurs immediately (within seconds to minutes). Immune response in this type is mediated largely by *humoral antibodies* (B cell-mediated). Immediate type of hypersensitivity reactions includes *type I, II and III.*
b. Delayed type in which the reaction is slower in onset and develops within 24-48 hours and the effect is prolonged. It is mediated by the *cellular response* (T cell-mediated) and it includes *Type IV reaction* [5].

Mechanisms of Hypersensitivity Reaction: Humans live in an environment teeming with substances capable of producing immunologic responses. Contact with antigens leads not only to the induction of a protective immune response, but also to reaction that can be damaging to tissue Exogenous antigen occur in the dust, pollens, foods, drugs microbiologic agent, chemicals and many blood product used in clinical practice the immune responses that may result from such exogenous antigen take a variety of from ranging from annoying but trivial discomforts, such as itching of skin, to potentially fatal diseases, such as bronchial asthma. The various reactions produced are called hypersensitivity reactions, a tissue injury in the reaction may be caused by humoral or cell-mediated immune mechanisms.

Injurious immune reactions may be evoked not only by exogenous environmental antigens, but also by endogenous environmental antigens, but also by endogenous tissue antigens. Some of these immune reactions are triggered by homologous antigens that differ among individuals with different genetic backgrounds. Transfusion reactions and graft rejection are examples of immunologic disorders evoked by homologous antigens. Another category of disorders, those incited by self -, or autologous, antigens,

constitutes the important group of autoimmune diseases (discussed later). These diseases arise because of the emergence of immune responses against self–antigens [6].

Table 1 - Comparative Features of 4 Types of Hypersensitivity Reactions [5]

Feature	Type I [Anaphylactic, atopic]	Type II [Cytotoxic]	Type III [Immune-complex, Arthus reaction]	Type IV [Delayed hypersensitivity]
Definition	Rapidly developing immune response in a previously sensitized person	Reaction of humoral antibodies that attack cell surface antigen and cause cell lysis	Result from deposition of antigen-antibody complexes on tissues	Cell-mediated slow and prolonged response
Peak action time	15-30 minutes	15-30 minutes	Within 6 hours	After 24 hours
Mediated by	IgE antibodies	IgG or IgM antibodies	IgG or IgM antibodies	Cell-mediated
Examples	i. Systemic anaphylaxis. ii. Local anaphylaxis [hay fever, bronchial asthma, food allergy].	i. Cytotoxic antibodies to blood cells [autoimmune haemolytic anaemia, transfusion reactions]. ii. Cytotoxic antibodies to tissue components [Graves' disease, myasthenia gravis].	i. immune complex glomerulonephritis. ii. Goodpastures syndrome. iii. Collagen diseases [SLE, rheumataoid arthritis]. iv. PAN. v. Drug-induced vasculitis.	i. Reaction against microbacterial antigen [tuberculin reaction, tuberculosis]. ii. Reaction against virus-infected cells. iii. Reaction against tumour cells.

Autoimmune Diseases: Autoimmunity is a state in which the body's immune system fails to distinguish between 'self' and 'non-self' and reacts by formation of auto-antibodies against one's tissue antigens. In other words, there is a loss of tolerance to one's tissues; *autoimmunity is the opposite of immune tolerance* [5]. Depending upon the type of autoantibody formation, autoimmune diseases are broadly classified into two groups:

a. Organ-specific diseases: In these, the autoantibodies formed react specifically against an organ or target tissue component and cause its chronic inflammatory destruction. The tissues affected are endocrine glands (e.g. thyroid, pancreatic islets of Langerhans, and adrenal cortex), alimentary tract, blood cells, and various other tissues and organs.

b. Organ non-specific (Systemic) diseases: These are diseases in which several auto-antibodies are formed that react with antigens in many tissues and thus cause systemic lesions e.g. various systemic collagen diseases [5].

Possible immune disorders: These are the disorders in which the immunologic mechanisms are suspected in their etiopathogenesis. A classic example of this group is *amyloidosis.*

Immunomodulators

Immunomodulators: are natural or synthetic components that regulate the immun**e** system and induce innate and adaptive defense mechanisms. Immunomodulators are drugs or components that suppress the immune system (immunosuppressants) or stimulate the immune system (immunostimulants) [4].

Classification of Immunomodulators

Immunostimulants: immunostimulants are substances that stimulate the immune response or enhance body resistance against various infections by increasing the basal level of immune responses. Immunostimulants are used for the treatment of autoimmune diseases, chronic infections, viral infection, and cancer-like diseases.

There are two types of Immunostimulants

a. **Specific Immunostimulant:** It provides antigenic specificity in immune response e.g. antigen, vaccines.
b. **Non-Specific Immunostimulants:** It act irrespective of antigenic specificity to augments immune response of other antigen or stimulate components of the immune system without antigenic specificity e.g. Adjuvants.

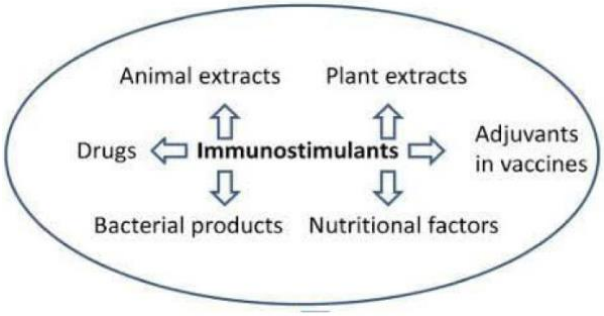

Figure 2 - Examples of Immunostimulants

Immunosuppression: Immunosuppression is a reduction of the activation or efficacy of the immune system. It is a phenomenon wherein the ability of an organism to form antibodies in response to an antigenic stimulus is reduced or suppressed. This suppression may be the result of a disease that targets the immune system, such as HIV infection or a consequence of pharmaceutical agents used to fight cancer. In some cases, immunosuppression may be deliberately induced. Induction may be required for therapeutic interventions of tissue or organ transplantation to reduce the risk of organ rejection. It is also used for treating graft-versus-host disease after a bone marrow transplant or for treatment of auto-immune diseases such as systemic lupus erythematosus, rheumatoid arthritis, Sjogrens syndrome or Crohn's disease [4].

Two types of immunosuppression

1. Non-specific immunosuppression: This immunosuppression invariably takes places, particularly in the natural instances related to immune deficiency disorders, or may even be induced by the gradual depletion of lymphoid tissue or by the administration of immunosuppressive drugs. It has been observed adequately that undue radiation exposure gives rise to significant depletion of lymphocytes.

2. Specific immunosuppression: - Specific immunosuppression is usually induced either by antigen or antibody. Azathiopurine and corticosteroid combination therapy is commonly used in tissue transplantation to inhibit cell-mediated immunity [CMI]. Cyclosporine is commonly used in immunosuppressive therapy. The monoclonal antibody [OKT3] is also used as an immunosuppressive agent after organ transplantation in humans [4].

Nutraceuticals: Nutraceuticals is defined as substances that can be considered food or its part which, in addition to their normal nutritional value provide health benefits including prevention of disease or promotion of health. The knowledge about the nutritive value of various food items and their basic chemical roles has increased [4].

Classification of Nutraceuticals

1. Nutraceuticals from food source: Nutraceuticals are obtained from plants, animals and microbial resources and are restricted to them only. Linolenic acid is found in animal flesh and is also synthesized in plants. Choline and aphosphatidyl choline are available in plants, animals, and also in microbes.

2. Nutraceuticals indicating their action of mechanism: Nutraceuticals indicate their pharmacological activities i.e. Anti-oxidants, Anti-inflammatory, Anti-cancer, Anti-bacterial, and Bone Protectives.

3. Nutraceuticals according to their chemical nature: The chemical nature of nutraceuticals is Phenolic compounds, Protein-based Isoprenoids, Carbohydrate derivatives, Fatty acids and structural lipids, microbial, minerals, etc.

4. Nutraceuticals according to their higher contents in specific food items: The food substances used as nutraceuticals contain antioxidants, prebiotics, probiotics omega-3-fatty acids, certains phytochemicals and dietary fibers. Expect probiotics, all these components are present in fruits, vegetables and different types of foods. [4]

Advantages of Nutraceuticals

a. They are substances like food and not considered drugs so have fewer side effects.
b. They are mainly used as preventive are prophylactic to improve medical conditions.
c. They have natural ingredients and dietary supplements to balance diet discrepancies.
d. They enhance overall health and well-being.
e. They are available without prescription means accessible and affordable [9].

Disadvantages of Nutraceuticals

a. **Quality and Regulation Issues:** As compared to pharmaceuticals, nutraceuticals are not regulated very strictly and directly. Some of the health claims made for nutraceuticals may not be scientifically validated. There is a lack of proper regulation for nutraceuticals.
b. **Bioavailability:** Nutraceuticals may have poor bioavailability and data related to pharmacokinetics and pharmacodynamics may not be available in some cases.
c. **Placebo effect:** The body has a mechanism to recover on its own. In such cases, consumers may not use nutraceuticals to treat ailments and have a placebo effect.
d. **Safety and Interactions:** Rarely, nutraceuticals may have some side effects. As there is a lack of appropriate regulations, there may be possible side effects, interaction with other drugs, or maybe in effectiveness in treating disorders [9].

Table 2 - A brief description of Immunomodulators derived from Nutraceuticals

Common Name	Botanical name (Family)	Part used	Chemical constituents	Other Biological Activity	Ref. no.
Tea	*Camellia sinensis* L. (*Theaceae)*	Leaves	Epigallocatechin gallate, Quercetin, Gallic acid	Anti-Oxidant	25
Tulsi	*Ocimum sanctum* L.*(Labiateae*)	Entire plant	Essential Oil such as eugenol,Cavacrol	Immunomodulator	8 (14.14)
Ginger	*Zingiber officinale roscoe (Zingiberaceae*)	Dried Rhizome	Camphene, Citral, Borneol, Cineolc	Anti-Oxidant	9 (4.39-4.42)
Garlic	*Allium sativum (Liliaceae)*	Bulbs	Diallyl disulfide, Diallyl trisulfide, Zinc, Vit-A	Anti-Oxidant Immunomodulator	9 (4.45-4.46)
Turmeric	*Curcuma langa (Zingiberaceae*)	Rhizome	Curcumin Hydrophobic	Anti-Oxidants Anti-Inflammatory	9 (7.6)
Amla	*Emblica officinalis gaetan (Euphorbiaceae)*	Fruit	Tannins, Punigluconin, pedunculagin	Anti-Oxidant	9 (4.50-4.51)
Pepper	*Piper nigrum (Piperaceae)*	Fruit	Volatile Oil, Guineensine, Limonenecamphene, Eugenol	Anti-Oxidant	9 (5.21)
Tomato	*Solanum lycopersicum (Solanaceae)*	Fruit	Lycopen, Lipophilic	Anti-Oxidant	9 (6.15)
Thyme	*Thymus vulgaris* L. *(Labiateae)*	Leaves	Flavonoids, Caffeic acid, Labiatic acid	Anti-Oxidant	8 (14.66-14.67)
Spirulina	*Spirulina plantensis (Oscillatoriceae)*	Algae	Proteinous nitrogen, lipid, Protein, Oleic	Immunostimulant	8 (18.9-18.10)
Echinacea	*Echinacea purpurea (Compositae)*	Leaf, flower	Arabinogalactan	Immunostimulant	8 (8.5)
Alfalfa	*Medicago sativa* Linn. *(Leguminosae)*	Herb	Vit.K, Vit.C, Thiamin, Riboflavin	Immunomodulator	9 (4.34-4.35)
Chicory	*Cichorium intybus* L. *(Asteraceae)*	Root	Sucrose, Cellulose, Protein, Volatile oil, Chicoric acid	Anti-Oxidant, Immunomodulator	9 (4.36-4.39)
Fenugreek (Methi)	*Trigonella foenumgraceum* L *(Fabaceae)*	Herb	Ascorbic acid, B Carotene, Fibers, Graicunins	Immunomodulator	9 (4.42-4.44)
Amra (mango)	*Mangifera indica* Linn. *(Anacardiaceae)*	Bark	Tannin, Catechin, Mangiferin	Anti- Oxidant	8 (10.3)
Ashoka	*Saraca indica* Linn. *(Leguminosae)*	Dried Stem Bark	Tannin, Haematoxylin, Ketosterol, Saponin	Immunostimulant	8 (10.14-10.16)
Ginseng	*Panax ginseng (Araliaceae)*	Root	Ginsenosides, Ginsenine, β-sitosterol	Anti-Oxidant, Immnomodulator	8 (9.50-9.52)

Ashvagandha	*Withania somnifera dunal (Solanceae)*	Root	Withanolides, Withaferin-A, Amino acids	Immunomodulator	9 (4.56-4.58)
Ginkgo Biloba	*Ginkgo biloba* L. *(Ginkgoaceae)*	Leaves	Quercitrin, Rutin, Kaempferol, Ginkgolide-A	Anti-Oxidant	9 (5.13-5.14)
Shatavari	*Aspargus racemosus wild (Liliaceae)*	Root	Shathavarin I-IV, Quercetin, Rutin	Anti-Oxidant	8 (9.62-9.63)
Milk-Thistle	*Milk thistle silybum marrianum gaerth (Compositae)*	Seed	Silymarin, Silybin, Silycrystin	Anti-Oxidant	8 (9.77-9.78)
Guduchi	*Tinospora cordifolia , Miers (Menispermaceae)*	Leave And Stem	Tinosporine, Tinosporic acid, Berberine	Immunostimulant	8 (9.101-9.103)
Rice Bran Oil	*Oryza sativa (gramineae)*	Seed	.Fatty acid, Palmitic Acid	Anti-Oxidant	8 (11.33-11.34)
Teel (Sesame)	*Sesamum indicum* Linn. *(Pedaliaceae)*	Seed	Mucilage, HCl, Fixed oil.	Anti-Oxidant, Anti-Inflammatory	7 (220)
Wormwood	*Artemisia annua* Linn. *(Compositea)*	Herb	Artemisinin	Immunosuppressive	10
Beggar-tricks	*Bidens pilosa* L. *(Asteraceae)*	Flower, Leave	Polyacetylenes	Anti-inflammatory , Immunosuppressive	11
Japanese Summer Grape Fruit	*Citrus nastudaidai hayata (Rutaceae)*	Fruit	Auraptene, Flavonoids	Antioxidant	12
Fig Marigold	*Carpobrotus edulis* L. *(Aizoaceae)*	Flower, Fruit	Alkaloids	Immunomodulator	13
Cone flower	*Echinacea angustifolia (Asteraceae)*	Flower	Polysaccharides	Immunomodulator	14
Bringraja	*Eclipta alba* L. *(Compositae)*	Leaves	Triterpenoids, Glucoside	Antioxidant	15
Sahijan	*Moringa oleifera* L. *(Moringaceae)*	Leaves	Vit.A, Carotenoids, Saponins	Antioxidant	16
Paarijaata Anti	*Nyctanthes arbortr tristis* L. *(Oleaceae)*	Leaf, seed	Iridoid glicoside	Inflammatory, Antispasmodic	17
Kutki	*Picrorhiza scrophulariiflora benth (Scrophulariaceae)*	Root	Iridoid glycoside, Amphicoside	Antioxidant	18
Roseroot	*Rhodiola imbricate gray (Crassulaceae)*	Rhizomes	Phenolics	Immunostimulating Property	19
Glasswort	*Salicornia herbacea (Chenopodiaceae)*	Herb	Polysaccharides	Immunomodulator	20
White cedar	*Thuja occidentalis* L. *(Arborvitae)*	leaves	Polysaccharide	Immunomodulator	21
Haussknechtia	*Haussknechtia elymatica (Apioideae)*	Herb	Phenolics	Immunomodulator	22

Cispanche	*Cistanche desertisola (Orobalachaceae)*	Herb	Polysaccharide	Immunomodulator	23
Brahmi	*Centella asiatica* Linn. *(Umbelliferae)*	Herb	Triterpenoids, Saponins	Immunomodulator	24
Dragon Head	*Dracocephalum kotschyi (Lamiaceae)*	Herb	Essential oil	Immunomodulator	25
Bay leaves (Tejpata)	*Cinnomomum tamala (Lauraceae)*	Leaves	Eucalyptol, Terpineol, Eugenol	Immunosuppressant	27
Cumin (jira)	*Cuminum cyminum* L. *(Apiaceae)*	Seeds	Cymol, Cuminol	Immunostimulant, Immunosuppressant	28
Tamarind (Imali)	*Tamarindus indica* L. *(Leguminosae)*	fruits	Compesterol, seven hydrocarbon, acetic acid, tartaric acid	Antioxidant, Immunomodulator	29, 30
Black Cumin	*Nigella sativa* L. *(Ranunculaceae)*	Seeds	Thymoquinone, Dithymoquinone	Immunomodulator	31
Bitter Melon (karela)	*Momordica charantia* L. *(Cucurbitaceae)*	Fruits , Seeds	Triterpene, proteid, steroid	Antioxidant, Immunostimunt	32
Key lime (lemon)	*Citrus aurantiifolia Swingle (Rutaceae)*	Fruits, Leaves	Limonene, Linalool, Citronellal	Antioxidant	33
Red Spiderling	*Boerhaavia diffusa* L. *(Nyctaginaceae)*	Roots	Boerhavia acid , Boeravinone, Palmitic acid	Antioxidant	34
Sea buckthorn	*Hippophae rhamnoides* L. *(Elaeagnaceae)*	Leaves, fruits	Quercetin derivatives, Hydrocinnamic acid	Antioxidant	35
Physic nut	*Jatropha curcas* L. *(Euphorbiaceae)*	Leaves	Phenolic acid, Lignans, Coumarins	Antioxidant, Immunomodulator	36
Sweet flag	*Acorus calamus* L. *(Araceae*)	Rhizome	Asarone, Monoterpene, Acorenone	Antioxidant, Immunosuppressive	37

Chemistry of plant-derived immunomodulators

1. **Glycosides:** These organic compounds from plant and animal sources, upon enzymatic or acid hydrolysis, yield one or more sugar moieties. Chemically, they are the acetals or sugar ethers, formed by the interaction of the hydroxyl groups of the sugar and non-sugar moieties, with the loss of a water molecule. Numerous glycosides have been shown to exert the desired immunomodulatory action [38].
2. **Flavonoids:** Chemically, flavonoids have a fifteen-carbon skeleton (C6-C3-C6) which consists of two phenyl rings connected by a three-carbon bridge. Several types of flavonoids exert immunomodulatory activities, including apigenin (3), oligomeric proanthocyanidins (4), isoflavonoids, flavones, and anthocyanidins. Such flavonoids are found in Terminalia Arjuna [38].
3. **Coumarins:** These glycosides are derivatives of benzo-a-pyrone (5); the furanocoumarins (6) are formed by fusion of furan ring to a coumarin at either the 6 and 7 position or the 7 and 8 position. These glycosides also exert immunomodulatory activities. These glycosides also exert immunomodulatory activites [39].
4. **Alkaloids:** These organic compounds are of natural or synthetic origin, basic in nature, containing one or more nitrogen atoms, normally heterocyclic, of limited distribution and have specific physiological actions on the human or animal body [39].

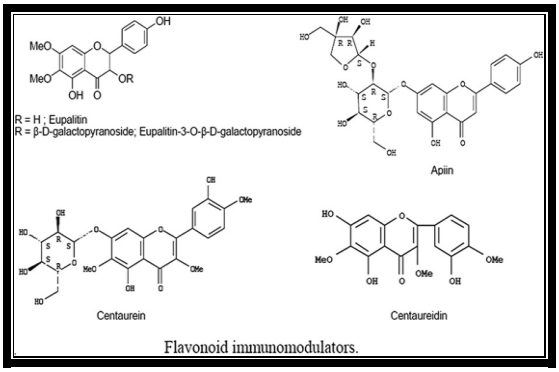

Figure 3 - Flavonoids showing immunomodulatory activity

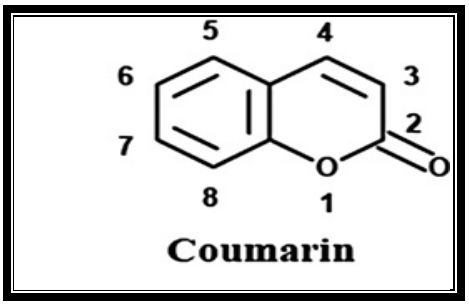

Figure 4 – Coumarin

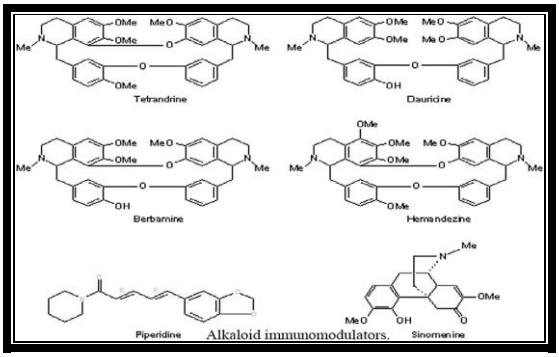

Figure 5 - Plant alkaloids with immunomodulatory activity

Concept of Rasayana

The word Rasayana, a combination of two words (rasa and ayana), refers to nutrition and its transportation throughout the body. Rasayana therapy enhances the qualities of rasa, enriching it with nutrients so one can attain longevity, improved memory and intelligence, freedom from disorder, youthfulness, excellence of hair, complexion and voice, optimum development of physique and sense organs, mastery over phonetics and brilliance. As a dedicated stream of medication for immune promotion, anti-degenerative and rejuvenating health care, the Rasayana therapy of Ayurveda is known to prevent the effects of ageing and improve the quality of life for healthy as well as diseased individuals. Rasayana is helpful to improve immunity and is normally advised during the degenerative phase of life, which starts from around 45 years in both male and female

Pharmacology of immunomodulatory activities from putative medicinal plants

Mechanism of action of the Rasayanas/ immunomodulators

It has been reported that the "Rasayanas" are rejuvenators, and nutritional supplements and possess strong antioxidant activities. They also exert antagonistic action on oxidative stressors, giving rise to the formation of different free radicals. They are used mainly to combat the effects of aging, atherosclerosis, cancer, diabetes, rheumatoid arthritis, autoimmune disease and Parkinson's disease. The Rasayana herbs seem to operate through immunostimulant, immunoadjuvant, and immunosuppressant activities or by affecting the effector arm of the immune response. [40] Modulation of the immune responses through the stimulatory or suppressive activity of a phyto-extract may help maintain a disease-free state in normal or unhealthy people. Agents that activate host defense mechanisms in the presence of an impaired immune response can provide supportive therapy to conventional chemotherapy. [41]

A high degree of cell proliferation renders bone marrow a sensitive target, especially to various cytotoxic drugs. Bone marrow is the organ most affected during any immunosuppression therapy with this class of drugs. Loss of stem cells and the inability of the bone marrow to regenerate new blood cells results in thrombocytopenia and leucopenia. [42] Many studies have reported the identification of immunomodulatory compounds with pharmacological activity and limited toxicity. In this context, ethnopharmacology represents the most important way possible to uncover interesting and therapeutically helpful molecules. The phytochemical analysis of Rasayana plants has revealed a large number of compounds including tannic acid, flavonoids, tocopherol, curcumin, ascorbate, carotenoids, polyphenols, etc., which have been shown to have potent immunomodulatory properties. The herbal mixture preparations of Indian traditional medicine may stimulate immunomodulation due to the content of plants with immunomodulatory properties that probably act synergistically. This hypothesis along with the lack of toxicity can be important to understand their use in the past as well as currently. [43]

CONCLUSION

The immune system is a complex organ with highly specialized cells and even a circulatory separate from blood vessels. Immunodeficiencies occur when one or more of the components of the immune system are inactive. Immunomodulation is the ruling of immune responses by stimulating them to prevent transmittable diseases or by suppressing them in undesired circumstances. Many proteins, amino acids, and natural compounds have shown a significant ability to regulate immune responses, including interferon-γ (IFN-γ), steroids, and DMG. Several medicinal

plants exhibit not only immunomodulatory activity but also a wide range of antioxidant, anti-inflammatory, and other medicinal activities. New immunomodulatory plants are important for the discovery of drugs with fewer side effects, less costly, more potent, and effective treatments developed for immune and related diseases.

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REFERENCES

1. Harshad Patel. A Focus on Hepatoprotective and Immunomodulatory Nutraceuticals.2007; 1-5.
2. Sharma PV, Dravyaguna Vigyan, Chowkambha Sanskrit Sansthan, 2001; 115.
3. Mukherjee PK, Nema NK, Bhadra S, Mukherjee D, Braga FC, Matsabisa MG. Immunomodulatory leads from medicinal plants. 2022; 05:51-56.
4. Chandrakant Kokare Pharmaceutical Biotechnology, Nirali Prakashan 2019; 1st Edi. :9.9 - 9.11.
5. Harsh Mohan, Textbook of Pathology, Jaypee Brother's :Med Publishers (P) LTD, 2010; 6th Edi. 61-82.
6. Robbins and Cotran, Pathologic Basic of Disease Kumar Abbas, Path; 2005, 7th Edi.: 194-205.
7. Trease, Evans Wallis Textbook of Pharmacognosy, CBS Publication.2005; 5th Edi.: 220.
8. CK Kokate, AP Purohit, SB Gokhale. Pharmacognosy Nirali prakashan 2019, 52ndEdi.:8.5-18.10
9. VM Shinde, KS Bodas-Yadav, Herbal Drug Technology, Nirali Prakashan, 2019 1st Edi.: Page no. 4.39-4.58, 7.6
10. Noori S, Naderi GA, Hassan ZM, et al. Immunosuppressive activity of a molecule isolated from Artemisia annua on DTH response compared with cyclosporine A. Int Immunopharmacol 2004;(10-11):1301-6.
11. Chang SL, Chiang YM, Chang CLT, et al. Flavonoids Centaurein and Centaureidin, From Bidens Pilosa, stimulate IFN expression. J Ethanopharmacol, 2007; 112:232-6.
12. Tanaka T, sugiura H, Inaba R, et al. Immunomodulatory action of citrus auraptene on macrophage function and cytokine production of lumphocytes in female BALB/c mice. Carcinogenesis, 1999; 20(8):1471-6.
13. Ordway D, Hohmann J, Viveiros M, et al. Carpobrotus edulis methanol extract inhibits the MDR efflux pump, enhance killing of phagocytoseds aureus and promote immune modulation phytother Res, 2003;(7(5):512-9.
14. Senchina DS, Mccann DA, Asp JM, et al. changes in immunomodulatory properties of Echinaceae spp root infusion and tincture stored at 4 degree C for four day. Clinica Chimica. Acta; 2005; 355 (1(2):67-82.
15. Jayathirtha MG, Mishra SH. Preliminary immunomodulatory activities of methanol extract of Eclipta alba & centella asiatica. Phytomedicine 2014; 11:361-5.
16. Gupta A, Gautam MK, Singh RK, et al. Immunomodulatory effect of Moringa Oleifera extract on Cyclophosphamide induced toxicity in mice. Ind J Exp Biol,2010;48.1150-67.
17. Kannan M, AJA Ranjit Singh, Ajith Kumar TT, et al. Studies on immnobioactivites of Nyctanthes arbortristis (Oleaceae) Afr J Microbiol Res 2007; 1(6);88-91.
18. Smit HF. Picrorhiza Scrophularii Flora From tranditional use to immunomodulatory activity. Utrecht, Netherlands: university of Utrecht, 2000. Journal No. 63975.
19. Mishra KP, Padwad YS, Dutta A, et al. Aqueous extract of Rhodiola imbricata rhizome inhibits proliferation of an erythroleukemic cell line K-562 by inducing apoptosis and cell cycle arrest at G2/M phase. 2008; 213(2):125-31.
20. Im SA, Kim K, Lee CK. Immunomodulatory activity of polysaccharide isolated from salicornia herbacea. Int Immunopharmpharmacol 2006; 6(9):1451-8.
21. Gohla SH, Zeman RA, Bagel M, et al. modification of the *in-vitro* replication of the human immunodeficiency virus HIV-1 TPSg a polysaccharide fraction isolated from the Cupressaceae Thuja Accidentalis L Arborvitae. Haematol Blood Transfus 1992; 35:140-9.
22. Amirghofran Z, Azadmeh A, Javidnia K. Haussknechtia Elymatica: A plant with immunomodulatory effects. Iran J Immunol 2007; 4(1):26-31.
23. Ebringerova A, Hromadkova Z, Hribalova V, et al. An immunomodulating pectic arabinogalactan from roots Cistanche deserticola. Chem Pap 2002; 56(5):320-5.
24. Mali RJ, Hatapakki BC. An in vitro study of effect of Centella asiatica on phagocytosis by human neutrophils. IJPSN 2008; 1(3): 297e 302.
25. Amirghofran Z, Azadbakht M, Karimi MH. Evaluation of the immunomodulatory effects of five herbal plants. J Ethnopharmacol, 2000; 72(1-2): 167-72.
26. Bhatt Rp, Pandya BK, Sheth RN. Camellia a sinensis L: the medicinal beverage a review IJPSRR. 2010; 3(2): 6-9.
27. M Shah, M Panchal. Ethnopharmacological properties of Cinnamomum tamala- A review. Inter J Pharmaceutical Sci Review and Res. 2015, (3), 141-144.
28. Dhruya R Jani, Hitesh. A review on herbal medicinal plants as natural immunomodulatory from the Indian kitchen A Solanki Publication. IJGHC. 2021; 10(3): 116.
29. Sreelekha TT, Vijayakumar T, Ankanthil R, et al. Immunomodulatory effects of a polysaccharide from Tamarindus indica, Anticancer. 4(1993) 209-212.
30. Librandi APL, Chrysostomo TN, Azzolini AECS, et al. Effect of the extract of the tamarind (Tamarindus indica) fruit on the complement system: Studies *in vitro* and in hamsters submitted to a cholesterol- enriched diet, Food Chem Toxicol, 45 (2007) 1487-1495.

31. Salem ML. Immunonodulatory and therapeutic properties of the Nigella sativa L seed Int Immunopharmacol. 2005;5:1749-1770.
32. Pongnikorn S, Fongmoon D, Kasinerk W et al. Effect of bitter melon (Momordica charantia Linn)on level and function of natural killer cells in cervical cancer patients with radiotherapy, J Med Assoc Thiland. 86 (2003) 61-68.
33. Gharagozloo M, Ghaderi A. Immunomodulatory effect of concentrated lime juice extract on activated human mononuclear cells, J Ethnopharmacol. 2001; 77: 85-90.
34. Mehrotra S, Mishra KP, Maurya R, et al. Immunomodulation by ethanolic extract of Boerhaavia diffusa roots, Int Immunopharmacol. 2002; 2: 987-996.
35. Geetha S, Singh V, Ram MS, et al. immunomodulatory effects of sea buckthorn against chromium (VI) induced immunosuppression, Mol Cell Biochem. 2005; 278: 101-109.
36. Abd-Allah HI, Moharram FA, Gaara AH et al. Phytoconstituents of jatropha curcas L. Leaves and there immunomodulatory activity on humoral and cell-mediated immune response in chicks. Zeitsschriftfur Narurforshhung, J Biosciences. 2009; 64: 495-501.
37. Mehrotra S, Misshra KP, Maurya R, et al. Anticellular and immunosuppressive properties of ethanolic extract of Acorus calamus rhizome, Intl Immunopharmaco. 2003; 3: 53-61.
38. Dinwsh Kumar, Vikrant Arya, Ranjeet Kaur, et al. A review of immunomodulators in the Indian traditional health care system. 170-172.
39. Kokate CK, Purohit AP, Gokhale SB. A Text Book of Pharmacognosy. 29th ed. Mumbai: Nirali Prakashan; 2004; 167,231
40. Chulet R, Pradhan P. A review on rasayana. *Phcog Rev* 2010; 3(6): 229-34.
41. Wagner H. In: Hikino H, Farnsworth NR, editors. Economic and medicinal plant research, vol. 1. London: Academic Press; 1984; 113e53.
42. Bafna AR, Mishra SH. Immunostimulatory effect of methanol extract of Curculigo orchioides on immunosuppressed mice. J Ethnopharmacol. 2006; 104:1e4.
43. Blasdell KS, Sharma HM, Tomlinson JPF, et al. (1991) Subjective survey, blood chemistry and complete blood profile of subjects taking Maharishi Amrit Kalash (MAK). Fed American Soc Exp Biol 5(5):A1317(2014).

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