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AN OVERVIEW ON IMMUNOMODULATORS

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ABSTRACT

The immune system is a complex and highly developed system in the body. The immune system is a part of body to detect the pathogen by using a specific receptor to produce immediately response by the activation. Immunomodulators are naturally present in the body, and certain of these are available in pharmacologic preparations. Immunomodulators correct immune systems that are out of balance. Some Immunomodulators are naturally present in the body, and certain of these are available in pharmacologic preparations. Knowledge of the mechanism of action of drugs provides targeted drug therapies so, synthetic immunomodulator drugs with their mechanism of action and uses have been listed out. Many botanical species have reported the immunomodulatory activity. It is based on the type of constituents present in the plant extracts so the list of Herbal plants with their chemical constituents and possible mechanism of action has been listed out. This review is an attempt to provide information regarding immune system and immunomodulatory agents.

Key words: Immune system, Immunomodulators.

INTRODUCTION

Immune system is a remarkably sophisticated defence system within vertebrates, to protect them from invading agents. It is able to generate varieties of cells and molecules capable of recognizing and eliminating limitless varieties of foreign and undesirable agents. Modulation of the immune system denotes to any change in the immune response that can involve induction, expression, amplification or inhibition of any part or phase of the immune response. Thus, immunomodulator is a substance used for its effect on the immune system. Immunopharmacology is a comparatively new and developing branch of pharmacology aims at searching for immunomodulators [1].

IMMUNE SYSTEM

Immune system is designed to protect the host from invading pathogens and to eliminate disease [2]. This ability enables the body to fight or prevent infectious disease and inhibit tissue and organ damage [3]. There are two types of immune response are occurs in the human body:

Immunomodulators

An Immunomodulator may be defined as a substance, biological or synthetic, which can stimulate, suppress or modulate any of the components of the immune system including both innate and adaptive arms of the immune response [5]. Immunomodulators are natural or synthetic substances that help regulate or normalize the immune system [6].

Clinically immunomodulators can be classified into following three categories: [7]

- Immunoadjuvants
- Immunostimulants
- Immunosuppressants

Immunoadjuvants: A non specific substance acting to enhance the immune response to an antigen with which it is administered. The immunoadjuvants hold the promise of being the true modulators of immune response [8].

Immunostimulants: Agents which are envisaged to enhance body's resistance against infections, they can act through innate immune response and through adaptive

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immune response [9].

Immunosuppressants: Agents which suppress the immune system and are used for the control of pathological immune response in autoimmune disease, graft rejection etc. [6].

Drugs Used For Immunomodulators

All drugs which modify immune response generally categorized as immunomodulators and also used for the prevention (or) cure of some infective conditions and also in management of cancer. These can either function as:

1. Immunosuppressants.
2. Immunostimulants.

Immunosuppressant Drugs

These are used to dampen the immune response in organ transplantation and autoimmune disease [6].

Immunostimulant Drugs

In contrast to immunosuppressive agents that inhibit the immune response in transplant rejection and autoimmunity, a few immunostimulatory drugs have been developed with applicability to infection, immunodeficiency, and cancer. These works on cellular as well as humoral immune system or both [6].

Herbal Plants as Immunomodulators

Herbal Plants have been used since ancient times for the treatment of various diseases and disorders. Plants with immunomodulators activity are reported in detail below as per the parts used: Fruits, Leaves, Seeds, Flowers, Roots, Bark.

Table 1. Types of Immune response

1.	Innate immune response	Response is non-specific. Exposure leads to immediate maximal response.
2.	Adaptive immune response	Pathogen and antigen specific response. Lag time between exposure and maximal response. Exposure leads to immunological memory. Cellular mediated response & humoral response.

Table 2. The Cells of the Immune System: [4]

CELL TYPE	FUNCTION
Helper T cell (CD4+T cell)	Commander of the immune response; detects infection and sounds the alarm, initiating both T cell and B cell responses.
Inducer T cell	Not involved in the immediate response to infection; mediates the maturation of other T cells in the thymus.
Cytotoxic T cell	Detects and kills infected body cells; recruited by helper T cells.
Suppressor T cell (CD8+T cell)	Dampens the activity of T and B cells, scaling back the defense after the infection has been checked.
B cell	Precursor of plasma cell; production of antibodies in response to foreign proteins of bacteria, viruses, and tumor cells.
Plasma cell	Biochemical factory devoted to the production of antibodies directed against specific foreign antigens.
Mast cell	Initiator of the inflammatory response which aids the arrival of leukocytes at a site of infection; secretes histamine and is important in allergic responses.
Monocyte	Precursor of macrophage.
Macrophage	The body's first cellular line of defense; also serves as antigen-presenting cell to B and T cells and engulfs antibody covered cells. Important in the regulation of immune response.
Natural killer cell	Function as effector cell. Recognizes and kills infected body cells; natural killer (NK) cell detects and kills cells infected by a broad range of invaders; killer (K) cell attacks only antibody-coated cells.
Dendritic cell	It orginate in the bone marrow, function as antigen presenting cells (APC). These cells are found in the structural compartment of the lymphoid organs. These cells bind high amount to HIV.
Granulocytes (or) Polymorphonuclear (PMN) Leukocytes	Granulocytes are composed of three cell types identified as neutrophils, eosinophils and basophils. These cells are predominantly important in the removal of bacteria and parasites from the body. They engulf these foreign bodies and degrade them using their powerful enzymes.

Table 3. Classification of Immunosuppressants

DRUG	SITE OF ACTION	THERAPEUTIC USE
Glucocorticoids	Inhibitors of lymphocyte gene expression.	Acute transplant rejection, graft-versus-host disease in bone marrow transplantation, rheumatoid and other arthritides.
Cyclosporine	Calcineurin inhibitors & inhibitors of lymphocyte signaling.	Kidney, liver, heart, and other organ transplantation, rheumatoid arthritis and psoriasis.
Tacrolimus	Calcineurin inhibitors & inhibitors of lymphocyte signaling.	Prophylaxis of solid-organ allograft rejection, kidney transplantation.
Sirolimus	Inhibitors of lymphocyte signaling & mTOR (mammalian target of rapamycin) Inhibitors.	Organ transplant inhibitor, graft rejection, incorporated into stents to inhibit local cell proliferation.
Azathioprine	Cytotoxic Agents to reduce lymphocyte proliferation & Antimetabolites.	Allogeneic kidney transplantation, organ transplant rejection.
Mycophenolate Mofetil	selectively inhibits lymphocyte proliferation and functions including antibody formation, cellular adhesion, and migration.	Prophylaxis of transplant rejection, renal transplantation.
Cyclophosphamide	immunosuppressant as it suppresses B-lymphocyte proliferation but can enhance T-cell responses.	Autoimmune disorders in patients with acquired factor XIII antibodies and bleeding syndromes, autoimmune hemolytic anemia, Wegener's granulomatosis.
Etanercept	Prevent TNF α from binding to membrane bound TNFR1 &$TNFR_2$	Rheumatoid arthritis, psoriatic arthritis.
Infliximab	Cytokines inhibitors& Chimeric monoclonal antibody obtained by exposing the mice to human TNF- α, prevent the release of other proinflammatory cytokines.	It currently used in Cronh's disease and rheumatoid arthritis.
Adalimumab	Cytokine inhibitors & human recombinant monoclonal antibody to TNF-α.	Rheumatoid arthritis.
Antithymocyte Globulin (ATG)	Antibodies Against Specific Immune Cell Molecules & polyclonal antibodies.	Acute renal transplant rejection, recovery from ischemic reperfusion injury.
Muromunab	Monoclonal antibodies.	Acute organ transplant rejection.

Table 4. Classification of Immunostimulants

DRUG	SITE OF ACTION	THERAPEUTIC USE
Bacillus Calmette-Guerin (BCG)	Antigen processing and / or recognition	Treatment and prophylaxis of carcinoma of the urinary bladder, prophylaxis of primary and recurrent stage Ta and/or T1 papillary tumors after transurethral resection.
Levamisole	Antibody production (inhibition of interleak 1-2 production), amplification, antigen processing/ recognition.	Adjuvant therapy with 5-fluorouracil after surgical resection in patients with Duke's stage C colon cancer, agranulocytosis.
Thalidomide	Decrease circulating TNF-α in patients with erythema nodosum leprosum, but to increase it in patients who are HIV-seropositive.	Severe, refractory rheumatoid arthritis.
Recombinant cytokines:		
TYPES	**MODE OF ACTION**	**THERAPEUTIC USES**
Interferons	Induction of certain enzymes, inhibition of cell proliferation, and enhancement of immune activities, including increased phagocytosis by macrophages and augmentation of specific cytotoxicity by T lymphocytes.	Hairy cell leukemia, malignant melanoma, follicular lymphoma, AIDS related Kaposi's sarcoma, chronic hepatitis B and condylomata acuminate.
Interleukins	Cellular immunity is profoundly activated with lymphocytosis, eosinophilia,	Metastatic renal cell carcinoma and melanoma.

	thrombocytopenia, and release of multiple cytokines.	
Colony stimulating Factor	Increases the number and differentiation of myeloid progenitors.	Leucopenia, ganciclovirinduced neutropenia.
DRUG	**SITE OF ACTION**	**THERAPEUTIC USES**
Isoprinosine	Increases proliferation of lymphocytes in response to mitogenic or antigenic stimuli, increases active T-cell rosettes and induces T-cell surface markers on prothymocytes.	Herpes simplex infections, subacute sclerosing panencephalitis, acute viral encephalitis caused by herpes simplex, Epstein-Barr and measles viruses.
Immunocynin	Stable form of haemocynin, a non-haeme, oxygen carrying, copper-containing protein found in arthropods and molluses.	Urinary bladder cancer.

Table 5. List of Plants Investigated Pharmacologically For Immunomodulatory Activity

BOTANICAL SOURCE	CHEMICAL CONSTITUENT	IMPACT FACTORS
FLOWERS		
Couropita guianensis (Lecythidaceae) [10]	Steroids, Phenolics, flavonoids, glycosides, carbohydrates and protiens.	Immunostimulant activity on both specific and non-specific immune mechanisms.
Hibiscus sabdariffa (Malvaceae) [11]	----	Immunostimulatory activity with increase in production of Anti-inflammatory cytokine, IL-10 and reduction in tissue necrosis factor –alpha.
Azadirachta indica (Meliaceae)[12]	----	Stimulates both specific and nonspecific immune responses. Potent immunostimulant against cytotoxic drug.
ROOTS		
Withania somnifera (Solanaceae) [13]	Steroidal Lactones (Withanolides), Polysaccharides, lectins, Proteins and peptides.	Immunomodulator to counteract undesirable effects of myelosuppressive drugs. Stimulates the haemopoetic system and also enhances the differentiation of stem cells.
Boerhavia diffusa (Nyctaginaceae) [14]	Alkaloids, carbohydrates, glycosides, triterpenoids, steroids, phenols and tannins.	Roots possess antistress, adaptogenic and immunopotentiating activity.
Calophyllum brasiliense (Clusiaceae) [15]	-----	Immunostimulant.
Clerodendrum phlomidis [16]	B-sitosterol & γ-Sitosterol, Cetyl alcohol, Clerodin, Clerosterol, Clerodendrin, Flavonoids-Pectolinarigenin, Hispidulin, Apigenin, luteolin.	Immunomodulator. (Higher response to specific immunity as compared to non specific immunity)
Premna integrifolia [16]	Premnine, Ganikarine, Premnazole, Flavonoids, luteolin, sterols and terpenes.	Immunomodulator. (Higher response to specific immunity as compared to non specific immunity)
Baliospermum montanum (Euphorbiaceae) [17]	Tannins, Saponins, Flavonoids, Glycosides.	Immunostimulant.

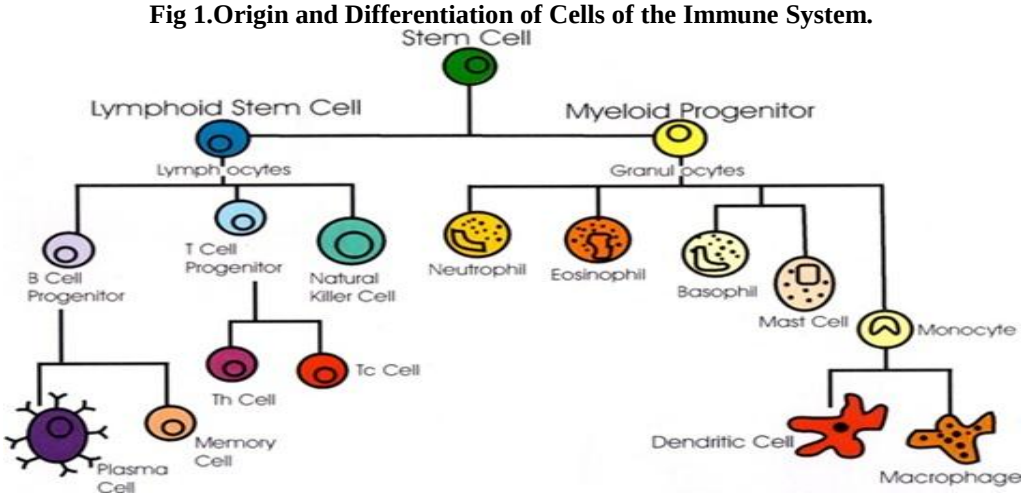
BOTANICAL SOURCE	CHEMICAL COUNSTITUENTS	IMPACT FACTORS
LEAVES		
Ocimum sanctum (Lamiaceae) [18]	Ascorbic acid and flavonoids	Ascorbic acid and flavonoids isolated from the leaf possess potent immunostimulant activity, but in combination showed synergistic activity it might

		be due to antioxidant property.
Aloe vera (Liliaceae) [19]	------	Potential candidate in several immunosuppressed clinical conditions.
Cassia auriculata (Caesalpiniaceae) [20]	Pet. Ether extract-steroids Alcoholic & Aqueous Extract-Alkaloids, Flavonoids, Tannins, Phenolics.	Significant immunostimulant effect on cell mediated immunity and no effect on Humoral immunity.
Tridax procumbens (Compositae) [21]	Flavones, Glycoside, Polysaccharide, Monosaccharide, Asteraceae.	Stimulatory effect on humoral immunity and stimulated phagocytosis and offered protection against P. aeruginosa infection.

SEEDS		
Mucuna Pruriens (Fabaceae) [22]	-------	It produces inhibitory effect and suggests its use in inflammatory disorders.
FRUITS		
Trapa bispinosa (trapaceae) [23]	Alkaloids, carbohydrates, starch, tannins, phenolic compounds & saponin glycosides.	Promising immunostimulatory activity.
Terminalia belerica (Combretaceae) [24]	Gallic acid, ellagic acid, ethyl gallate, chebulic acid, β-sitosterol, 3-lignans & one flavan.	T. belerica shows immunosuppressant effect at low concentration while stimulatory activity at high concentration.
BARK		
Alstonia boonei (Apocyanaceae) [25]	Alkaloids – Indole, terpenes, lactones & Steroids, Triterpenes – a & b ammyrin & lupeol.	Anticomplementary action may be beneficial in rheumatoid arthritis.
Acacia catechu (Leguminosae) [26]	Catechin and epicatechin.	The aqueous extracts of Acacia catechu have significant effect on both the cell mediated and the humoral immunity. Low dose was more effective as compared to the higher dose.
Bauhinia variegata (Caesalpiniaceae) [27]	Tannins, steroids, alkaloids, flavonoids, β sitosterol, lupeol, vitamin C, kaempferol, flavones, quercetin & saponins.	Immunostimulant activity on both specific and non-specific immune system.
Matayba elaegnoides (Sapindaceae) [15]	--------	Immunostimulant.
AERIAL PARTS		
Alternanthera tenella Colla (Amaranthaceae) [28]	Fatty acids, flavonoids, polysaccharides, tritepenes, Glycosides & saponins.	Inhibitory action on B-lymphocyte fuction, Reduce antibody production to T-dependent antigen, Simultaneous immunostimulatory and immunosuppressive activity.
Hyptis suaveolens (Lamiaceae)[29]	Volatile Oil	Immunostimmulant.
Dittrichia viscose (Asteraceae)[30]	Flavonoids	Immunomodulatory effect.
Aster squamatus (Asteraceae)[30]	Flavonoids	Immunomodulatory effect.
Glebionis coronaria (*Asteraceae)* [30]	Flavonoids	Immunomodulatory effect.
Calendula arvensis (*Asteraceae)* [31]	Flavonoids	Immunomodulatory effect.
Carlina involucrate (*Asteraceae)*	Flavonoids	Immunomodulatory effect.
Galactities tomentosa (*Asteraceae)*	Flavonoids	Immunomodulatory effect.
Inula crithmoides	Flavonoids	Immunomodulatory effect.

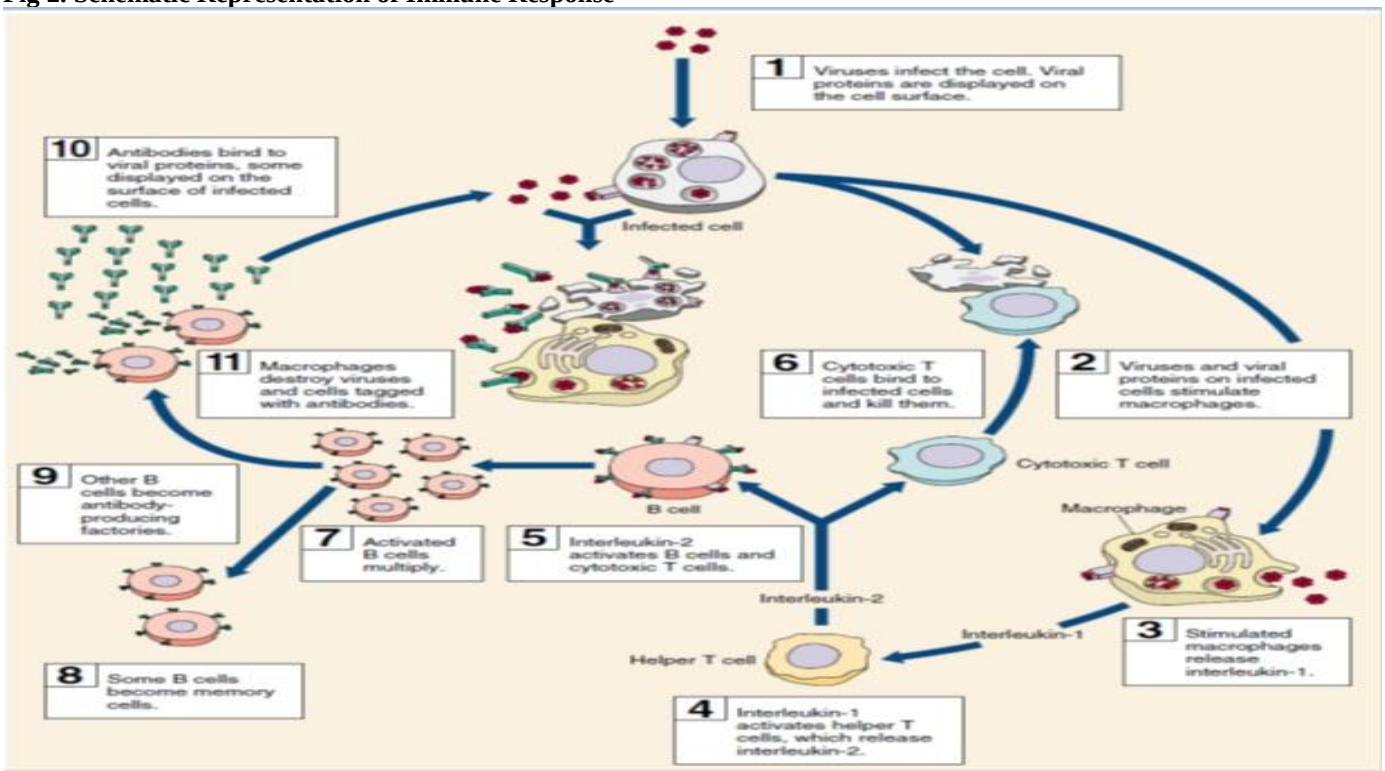
(Asteraceae)		
Leontodon tuberosus (Asteraceae)	Flavonoids	Immunomodulatory effect.
Reichardia picroides (Asteraceae)	Flavonoids	Immunomodulatory effect.
Sonchus oleraceus (Asteraceae)	Flavonoids	Immunomodulatory effect.
WHOLE PLANT [31]		
Ipomea pes caprae(Convolvulaceae)	------	Immunostimulant.

Fig 1.Origin and Differentiation of Cells of the Immune System.



Immune Response

Fig 2. Schematic Representation of Immune Response



CONCLUSION

Immunomodulators are becoming very popular in the worldwide natural health industry as people start to realize the importance of a health immune system in the maintenance of health and the prevention of disease. This review provides the information regarding mechanism, cells that are involved and both synthesis as well as herbal immunomodulators in one window.

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