Original Article

An Overview of Immunology - Systemic Review

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ABSTRACT

Immunology is one of the most rapidly developing areas of medical biotechnology research and has great promises with regard to the prevention and treatment of a wide range of disorders such as the inflammatory diseases. In addition, infectious diseases are now primarily considered immunological disorders, while neoplastic diseases and organ transplantation and several autoimmune diseases are involved in an immunosuppressive state. Immunomodulators are natural or synthetic substances that help regulate or normalize the immune system. Immunomodulators correct immune systems that are out of balance. The benefits of immunomodulators stem from their ability to stimulate natural and adaptive defense mechanisms.A number of disorders such as immunodeficiency state, autoimmune disease, cancer and viral infection can be treated with immunostimulants drugs. The immune system is a part of body to detect the pathogen by using a specific receptor to produce immediately response by the activation of immune components cells, cytokines, chemokines and also release of inflammatory mediator. They modulate and potentiate the immune system.

Keywords: Immunomodulators, Immunosuppressive, Immunology.

INTRODUCTION

The immune system is designed to protect the host from invading pathogens and to eliminate disease. The primary object in the past has been to suppress immune system to permit allotransplantation. Activation of immune system by “non-self” antigen (alloantigen) or “self” antigen (auto antigen) is generally believed to require processing of the antigen by the phagocytic cells such as macrophages, monocytes, or related cells. There are two types of immune response are occurs in the human body:

I) Innate immune response
II) Adaptive immune response
  a. Humoral immunity
  b. Cellular immunity

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I) Innate immune response: The innate immune response is the first line of defense mechanism against physical, biochemical and cellular components.

II) Adaptive immune response:

a) Humoral immunity - Antibody production – killing extracellular organisms.

b) Cell mediated immunity – cytotoxic / killer T-cells – killing virus and tumour cells. Cellular immunity is expressed as cytotoxicity towards target cells by activation of cytotoxic or "killer" T-cells. The action of the cytotoxic T-cell is also inhibited by adrenocorticosteroids[1]. But the humoral arm of the immune response is responsible for the production of the antibodies; this is carried out by cells derived from the bone marrow (β-cell).

Immunity[2]

This may be defined as the body's ability to identify and resist large numbers of infectious and potentially harmful microorganisms, enabling the body to prevent or resist diseases and inhibit organ and tissue damage[2]. The immune system is not confined to any one part of the body. Immune stem cells, formed in the bone marrow, may remain in the bone marrow until maturation or migrate to different body sites for maturation. Subsequently, most immune cells circulate throughout the body, exerting specific effects. The immune system has two distinct but overlapping mechanisms with which to fight invading organisms, the antibody-mediated defense system (humoral immunity) and the cell-mediated defense system (cellular immunity).

Immune systems[3,4,5]

The basic architecture of the immune system is multilayered, with defenses on several levels. Most obvious and primary is the skin: the first barrier against infection. Another is physiological, where conditions like the temperature and pH of the body provide inappropriate living conditions for foreign organisms. Once pathogens have successfully entered the body, they are addressed by the innate and/or the acquired or adaptive immune system[3]. Both systems consist of a multitude of cells and molecules that interact in a complex manner to detect and eliminate pathogens[4]. Detection and elimination depend upon chemical bonding: surfaces of immune system cells are covered with various receptors, some of which chemically bind to pathogens, while others bind to other immune system cells or molecules to enable the complex signaling system that mediates the immune response[5].

Immunomodulators[6]

These are biological or synthetic substances that can stimulate, suppress or modulate any aspect of the immune system including both adaptive and innate arms of the immune system[6].

Classification of immunomodulators

Clinically, immunomodulators can be classified into the following three categories:

Immunoadjuvants are used to enhance the efficacy of vaccines and therefore could be considered specific immune stimulants. Immunoadjuvants hold the promise of being the true modulators of the immune response. It has been proposed that they be exploited as selectors between cellular and humoral helper T1 (Th1) and helper T2 cells (Th2), immunoprotective, immunodestructive, and reagenic [immunoglobulin E (IgE)] versus IgG type immune responsesdposing a real challenge to vaccine designers.

Immunostimulants[7] are inherently non-specific as they are envisaged as enhancements to a body's resistance to infection. They can act through innate as well as adaptive immune responses. In

healthy individuals, the immunostimulants are expected to serve as prophylactic and promoter agents, i.e., as immunopotentiators, by enhancing the basic level of immune response[7]. In the individual with impairment of immune response, they are expected to act as immunotherapeutic agents.

Immunosuppressants[3] are a structurally and functionally heterogeneous group of drugs, which are often concomitantly administered in combination regimens to treat various types of organ transplant rejection and autoimmune diseases.

Drugs used for Immunomodulation[8]

All drugs which modify immune response generally categorized as immunomodulators. These can either function as:

1. Immunosuppressants
2. Immunostimulants.

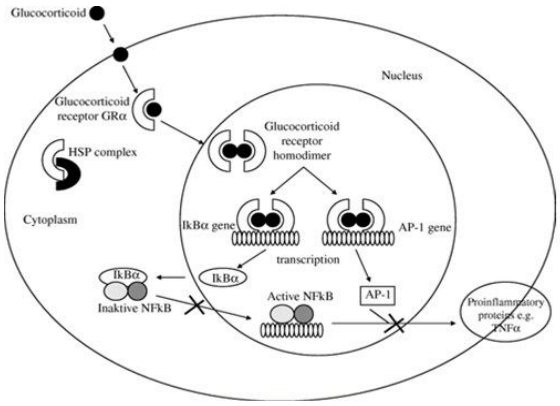
Some of these can have both the properties depending on which component of immune response they affect. There is also an upcoming generation of immunosuppressants called tolerogens.

1. Immunosuppressant drugs[8]

I. Inhibitors of Lymphocyte Gene Expression to Reduce Inflammatory Response Glucocorticoids:

Mechanism of Action[9,10]

Multiple mechanisms are involved in the suppression of inflammation by glucocorticoids. Glucocorticoids inhibit the production by multiple cells of factors that are critical in generating the inflammatory response. As a result there is decreased release of vasoactive and chemoattractive factors diminished secretion of lipolytic and proteolytic enzymes decreased extravasation of leukocytes to areas of injury and ultimately decreased fibrosis[9]. Glucocorticoids can also reduce expression of proinflammatory cytokines such as COX-2 and NOS2. The influence of stressful conditions on immune defense mechanisms is well documented as is the contribution of the HPA axis to the stress response. Stresses such as injury, infection and disease result in the increased production of cytokines a network of signalling molecules that integrate actions of macrophages /monocytes, T lymphocytes and B lymphocytes in mounting immune responses[10]. Among these cytokines interleukin (IL)-1, IL-6, and tumor necrosis factor-a (TNF-a) stimulate the HPA axis with IL-1 having the broadest range of actions. IL-1 stimulates the release of CRH by hypothalamic neurons, interacts directly with the pituitary to increase the release of ACTH and may directly stimulate the adrenal gland to produce glucocorticoids. Factors that are inhibited include components of the cytokine network, including interferon-g (IFN-g), granulocy-temacrophage colony-stimulating factor (GM-CSF), interleukins (IL-1, IL- 2, IL-3, IL-6, IL-8, and IL-12), and TNF-a.



Therapeutic Uses

Acute transplant rejection, graft-versus-host disease in bonemarrow transplantation, rheumatoid and other arthritides, systemic lupus erythematosus, systemic dermatomyositis, psoriasis and

other skin conditions, asthma and other allergic disorders, inflammatory bowel disease, inflammatory ophthalmic diseases.

Adverse Effects

Growth retardation in children, avascular necrosis of bone, osteopenia, increased risk of infection, poor wound healing, cataracts, hyperglycemia, and hypertension[11].

II. Inhibitors of Lymphocyte Signaling to Prevent Immune Cell Activation and Proliferationa)

Calcineurin Inhibitors

Cyclosporine

Cyclosporine (cyclosporin A), a cyclic polypeptide consisting of amino acids is produced by the fungus species *Beauveria nivea*.

Mechanism of Action[12]

Cyclosporine suppresses T-cell-dependent immune mechanisms such as those underlying transplant rejection and some forms of autoimmunity. It preferentially inhibits antigen-triggered signal transduction in T lymphocytes, blunting expression of many lymphokines including IL-2 and the expression of antiapoptotic proteins. Cyclosporine forms a complex with cyclophilin, a cytoplasmic receptor protein present in target cells. This complex binds to calcineurin, inhibiting Ca2+-stimulated dephosphorylation of the cytosolic component of nuclear factor for activated T-cells (NFAT)[12]. When cytoplasmic NFAT is dephosphorylated and translocates to the nucleus and complexes with nuclear components required for complete T-cell activation including transactivation of IL-2 and other lymphokine genes. Calcineurin phosphatase activity is inhibited after physical interaction with the cyclosporine/cyclophilin complex. This prevents NFAT dephosphorylation such that NFAT does not enter the nucleus gene transcription is not activated and the T lymphocyte fails to respond to specific antigenic stimulation. Cyclosporine also increases expression of transforming growth factor-b (TGF-b), a potent inhibitor of IL-2-stimulated T-cell proliferation and generation of cytotoxic T lymphocytes (CTL).

Pharmacokinetics[8]

Cyclosporine can be given orally or I.V. Its oral bioavailability is low (about 30%). Food decreases its absorption. It is metabolized by CYP3A which may result in drug-drug interactions. Inactive metabolites are excreted mainly in bile and then in feces but minimally in urine. Plasma half life is about 24 hrs.

Therapeutic Uses[13]

Kidney, liver, heart, and other organ transplantation, rheumatoid arthritis and psoriasis, early engraftment, extending kidney graft survival, cardiac and liver transplantation, Behcet's acute ocular syndrome, endogenous uveitis, atopic dermatitis[13].

Adverse effects

Renal dysfunction, tremor, hirsutism, hypertension, hyperlipidemia, gum hyperplasia, hyperuricemia, hyper-cholesterolemia, nephrotoxicity, hypertension, diabetogenic, Elevated LDL cholesterol.

Tacrolimus

Tacrolimus (PROGRAF, FK506) is a macrolide antibiotic produced by *Streptomyces tsukubaensis*.

Mechanism of Action[14]

Like cyclosporine, tacrolimus inhibits Tcell activation by inhibiting calcineurin. Tacrolimus binds to an intracellular protein FK506-binding protein-12 (FKBP-12) an immunophilin structurally related to cyclophilin. A complex of tacrolimus-FKBP-12, Ca2+, calmodulin, and calcineurin then forms, and calcineurin phosphatase activity is inhibited[14]. As described for cyclosporine the inhibition of phosphatise activity prevents dephosphorylation and nuclear translocation of NFAT and inhibits T-cell activation.

Pharmacokinetics

Tacrolimus can be given orally or I.V. It is 99% metabolized in liver by CYP3A and has a plasma half life of 7-8 hrs.

Therapeutic Uses

Prophylaxis of solid-organ allograft rejection, kidney transplantation, pediatric liver transplantation[15].

Adverse effects

Nephrotoxicity, neurotoxicity (tremor, headache, motor disturbances and seizures), GI complaints, hypertension, hyperkalemia, hyperglycemia, and diabetes .

b) Mammalian Target of Rapamycin (mTOR) Inhibitors[16]

Sirolimus

Sirolimus (rapamycin; RAPAMUNE) is a macrocyclic lactone produced by *Streptomyces hygroscopicus*

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Mechanism of Action[8]

Sirolimus inhibits T-lymphocyte activation and proliferation downstream of the IL-2 and other T-cell growth factor receptors. Sirolimus requires formation of a complex with an immunophilin in this case FKBP-12. However, the sirolimus-FKBP-12 complex does not affect calcineurin activity. It binds to and inhibits a protein kinase designated mammalian target of rapamycin (mTOR) which is a key enzyme in cell-cycle progression. Inhibition of mTOR blocks cell-cycle progression at the G1 to S- phase transition.

Pharmacokinetics

Oral bioavailability is 15%. Fatty meal decreases its bioavailability. Protein binding is 40-45% mainly with albumin. It is extensively metabolized in liver by CYP3A4. Sirolimus is excreted 91% in feces and only 2.5% in urine. Plasma half life is 62 hrs.

Therapeutic Uses

Organ transplant inhibitor, graft rejection, incorporated into stents to inhibit local cell proliferation and blood vessel occlusion.

Adverse Effects

Dose-dependent increase in serum cholesterol and triglycerides, impaired renal function, prolong delayed graft function, Lymphocele, anemia, leukopenia .

III. Cytotoxic Agents to Reduce Lymphocyte Proliferationa) Antimetabolites[17]

Azathioprine

Azathioprine (IMURAN) is a purine antimetabolite. It is an imidazolyl derivative of 6-mercaptopurine.

Mechanism of Action

Following exposure to nucleophiles such as glutathione, azathioprine is cleaved to 6-mercaptopurine, which in turn is converted to additional metabolites that inhibit de novo purine synthesis. 6-Thio-IMP, a fraudulent nucleotide, is converted to 6-thio-GMP and finally to 6-thio-GTP, which is incorporated into DNA[17]. Cell proliferation is thereby inhibited impairing a variety of lymphocyte functions.

Therapeutic Uses

Allogeneic kidney transplantation, organ transplant rejection.

Adverse effects

Bone marrow suppression including leukopenia (common), thrombocytopenia (less common), and/or anemia (uncommon), increased susceptibility to infections (especially varicella and herpes simplex viruses), hepatotoxicity, alopecia, GI toxicity, pancreatitis.

Mycophenolate Mofetil

Mycophenolate mofetil (CELLCEPT) is the 2-morpholinoethyl ester of mycophenolic acid (MPA).

Mechanism of Action

Mycophenolate mofetil is a prodrug that is rapidly hydrolyzed to the active drug, mycophenolic acid (MPA), a selective, noncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), an important enzyme in the de novo pathway of guanine nucleotide synthesis. B and T lymphocytes are highly dependent on this pathway for cell proliferation while other cell types can use salvage pathways; MPA therefore selectively inhibits lymphocyte proliferation and functions including antibody formation, cellularadhesion, and migration.

Pharmacokinetics

Mycophenolate mofetil undergoes rapid and complete metabolism to MPA after oral or intravenous administration. MPA, in turn is metabolized to the inactive phenolic glucuronide MPAG. Most (87%) is excreted in the urine as MPA.

Therapeutic Uses

Prophylaxis of transplant rejection, renal transplantation.

Adverse effects

Leukopenia, diarrhoea, and vomiting, sepsis associated with cytomegalovirus, in combination with mycophenolate mofetil has been associated with devastating viral infections including polyoma nephritis .

b) Alkylating Agents[8]

Cyclophosphamide

Cyclophosphamide is a unique immunosuppressant as it suppresses B-lymphocyte proliferation but can enhance T-cell responses.

Mechanism of Action

Alkylating agents introduce alkyl groups by forming covalent bonds with nucleophilic moieties such as phosphate, sulfhydryl, hydroxyl, carboxyl, amino and imidazole groups present in DNA or RNA. By cross linking in between the strands of DNA they prevent the cell division and protein synthesis. These drugs are most destructive to rapidly proliferating tissues and appear to cause cell death when they tend to divide. The cytotoxicity of these drugs correlates with the degree of DNA alkylation.

Therapeutic Uses

Autoimmune disorders (including systemic lupus erythematosus), in patients with acquired factor XIII antibodies and bleeding syndromes, autoimmune hemolytic anemia, antibody-induced pure red cell aplasia, and Wegener's granulomatosis.

Adverse effects

Pancytopenia and hemorrhagic cystitis, graftversus- host disease syndrome, nausea, vomiting, cardiac toxicity and electrolyte disturbances.

IV. Cytokine Inhibitors (Anticytokine-Antibodies)

TNF-α and IL-1 are proinflammatory cytokines implicated in pathogenesis of rheumatoid arthritis and Crohn's disease. Il-2 binds to activated T- -lymphocytes and promotes their proliferation.

TNF-α Inhibitors[18]

Activated cytotoxic TH1 cells, macrophages and cells secrete TNF-α that to TNF receptors (TNFR1 or TNFR2) present on fibroblasts, neutrophils and vascular endothelial cells. Besides these, there are soluble form of TNF-α receptor present in serum and synovial fluid. Activation of TNF-α result in the release of cytokines IL-1, IL-6 and adhesion molecules that promote leukocyte activation and trafficking (migration).

Etanercept[18]

Is genetically engineered fusion protein composed of two soluble TNFp75 receptors moieties linked to Fc portion of human IgG1. The drug serves as an exogenously administered soluble TNF-α receptor and provides artificial binding sites to TNF-α. This prevents TNF-α from binding to membrane bound TNFR1 and TNFR2. The drug is used primarily to treat rheumatoid arthritis, and psoriatic arthritis.

Infliximab[8]

Is a Chimeric monoclonal antibody obtained by exposing the mice to human TNF- α. The antibody so produced is then fused to constant region IgG1 to decrease the antigenicity of the drug. The drug cross links with membrane bound TNF—α receptors on cell surface to inhibit T-cell and macrophage function and to prevent the release of other proinflammatory cytokines (IL-1, IL-6 and 8 along with collagenase and metalloproteinases). Though it also has a longer half life, it does not bind TNF-β. It currently used in Cronh's disease and rheumatoid arthritis.

Adalimumab[8]

Is a human recombinant monoclonal antibody to TNF-α. It is less antigenic than Infliximab as it does not contain any foreign component. Its serum half life is 2 weeks. Patients of rheumatoid arthritis may therefore administer single dose of 40 mg/0.8 ml subcutaneously every 14 days 15.

V. Antibodies Against Specific Immune Cell Moleculesa)[8]

Polyclonal Antibodies

Antithymocyte Globulin (ATG)

Antithymocyte globulin is a purified gamma globulin from the serum of rabbits immunized with human thymocytes.

Mechanism of Action

Antithymocyte globulin contains cytotoxic antibodies that bind to CD2, CD3, CD4, CD8, CD11a, CD18, CD25, CD44, CD45, and HLA class I and II molecules on the surface of human T lymphocytes. The antibodies deplete circulating lymphocytes by direct cytotoxicity (both complement and cell-mediated) and block lymphocyte function by binding to cell surface molecules involved in the regulation of cell function.

Therapeutic Uses

Acute renal transplant rejection, recovery from ischemic reperfusion injury.

Adverse effects

Fever and chills, hypotension, Serum sickness, glomerulonephritis, leukopenia and thrombocytopenia, increased risk of infection and malignancy especially when multiple immunosuppressive agents are combined 4,15,18,20.

a) Monoclonal Antibodies[8,19]

Muromunab (Anti CD-3 Antibodies, OKT-3)

Antibodies directed at the chain of CD3, a trimeric molecule adjacent to the T-cell receptor on the surface of human T lymphocytes, have been used with considerable efficacy since the early 1980s in human transplantation.

Mechanism of Action

Muromonab-CD3 binds to the chain of CD3, a monomorphic component of the T-cell receptor complex involved in antigen recognition, cell signaling and proliferation. Antibody treatment induces rapid internalization of the T-cell receptor, thereby preventing subsequent antigen recognition. Administration of the antibody is followed rapidly by depletion and extravasation of a majority of T cells from the bloodstream and peripheral lymphoid organs such as lymph nodes and spleen. This absence of detectable T cells from the usual lymphoid regions is secondary both to cell death following complement activation and activation-induced cell death and to margination of T cells onto vascular endothelial walls and redistribution of T cells to nonlymphoid organs such as the lungs. Muromonab-CD3 also reduces function of the remaining T cells, as defined by lack of IL-2 production and great reduction in the production of multiple cytokines, perhaps with the exception of IL-4 and IL 10.

Therapeutic Uses

Acute organ transplant rejection.

Adverse effects

Cytokine release syndrome, high fever, chills/rigor, headache, tremor, nausea/vomiting, diarrhea, abdominal pain, malaise, myalgias, arthralgias, and generalized weakness. Less common complaints include skin reactions and cardiorespiratory and CNS disorders, including aseptic meningitis. Potentially fatal severe pulmonary edema, acute respiratory distress syndrome, cardiovascular collapse, cardiac arrest.

VI. Inhibitors of Immune Cell Adhesion:8,20

Efalizumab

Efalizumab (LFA-1 Inhibitor) is a humanized IgG1 mAb targeting the CD11a chain of LFA 1 (lymphocyte function associated antigen).

Mechanism of action

Efalizumab binds to LFA-1 and prevents the LFA-1-ICAM (intercellular adhesion molecule) interaction to block T-cell adhesion, trafficking, and activation.

Pharmacokinetics

Pharmacokinetic and pharmacodynamic studies showed that efalizumab produced saturation and 80% modulation of CD11a within 24 hours of therapy.

Therapeutic Uses

Survival of murine skin and heart allografts and monkey heart allografts, psoriasis, renal transplantation[20].

VII. Miscellaneous[-8]

Rho (D) Immune Globulin

Rho (D) immune globulin is a concentrated (15%) solution of human IgG containing a higher titer of antibodies against the Rho (D) antigen of the red cell.

Therapeutic uses

Hemolytic disease of the newborn.

2. Immunostimulants[21]

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.

I. Bacillus Calmette-Guerin (BCG)[8,22]

Live bacillus Calmette-Guerin (BCG; TICE BCG, THERACYS) is an attenuated, live culture of the bacillus of Calmette and Guerin strain of *Mycobacterium bovis.*

Mechanism of action

Induction of a granulomatous reaction at the site of administration.

Therapeutic uses

Treatment and prophylaxis of carcinoma of the urinary bladder, prophylaxis of primary and recurrent stage Ta and/or T1 papillary tumors after transurethral resection.

Adverse effects

Hypersensitivity, shock, chills, fever, malaise, and immune complex disease.

II. Levamisole[8]

Levamisole (ERGAMISOL) was synthesized originally as an anthelmintic but appears to restore depressed immune function of B lymphocytes, T lymphocytes, monocytes and macrophages.

Therapeutic uses

Adjuvant therapy with 5-fluorouracil after surgical resection in patients with Duke's stage C colon cancer, agranulocytosis.

Adverse effects

Flu-like symptoms, allergic manifestation, nausea and muscle pain 4.

III. Thalidomide[23]

Mechanism of action

Thalidomide has been reported to decrease circulating TNF-α in patients with erythema nodosum leprosum, but to increase it in patients who are HIV-seropositive. Alternatively, it has been suggested that the drug affects angiogenesis.

Therapeutic uses

Severe, refractory rheumatoid arthritis.

Adverse effects

Teratogenicity

IV. Isoprinosine[8]

Isoprinosine (Inosiplex) is a complex of the pacetamidobenzoate salt of N,N-dimethylamino-2- propanol: inosine in a 3:1 molar ratio.

Mechanism of action

Isoprinosine has been shown to augment production of cytokines such as IL-1, IL-2 and IFN-γ. It increases proliferation of lymphocytes in response to mitogenic or antigenic stimuli, increases active T-cell rosettes and induces T-cell surface markers on prothymocytes.

Therapeutic uses

Herpes simplex infections, subacute sclerosing panencephalitis, acute viral encephalitis caused by herpes simplex, Epstein-Barr and measles viruses,

Adverse effects

Minor CNS depressant, transient nausea and rise of uric acid in serum and urine.

Correlation of immunomodulators with Ayurveda

Ayurveda is a most ancient and yet currently vital tradition practiced widely in India, Sri Lanka and other countries. It has a sound philosophical and experimental basis. Atharvaveda (around 1200 BC), Charak Samhita and Sushrut Samhita (1000-500 BC) are the main classic reference collections that give a detailed description of over 700 herbs.

Concept of Rasayana[3]

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, antidegenerative 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 males and females.

Plants as immunomodulators[3]

Several medicinal plants used in the Indian traditional system known as Rasayana (devoted to enhancement of the body's resistance) have attracted the attention of scientists world-wide. As discussed below, several medicinal plants exhibit not only immunomodulatory activity but also a wide range of antioxidant, antiasthmatic, antiarrhythmic, antiinflammatory, hepatoprotective, hypocholesterolemic, antifungal, cardiotonic, diuretic, and other medicinal activities.

Pharmacology of immunomodulatory activities from putative medicinal plants[24]

Mechanism of action of the Rasayanas/ immunomodulators it has been reported that the "Rasayanas" are rejuvenators, 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 ageing, 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.Mechanisms of immunomodulation activity occur mainly via phagocytosis stimulation, macrophages activation, immunostimulatory effect on peritoneal macrophages, lymphoid cells stimulation, cellular immune function enhancement and nonspecific cellular immune system effect, antigen-specific immunoglobulin production increase, increased nonspecific immunity mediators and natural killer cell numbers, reducing chemotherapy-induced leukopenia, and increasing circulating total white cell counts and interleukin-2 levels. 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. Recently, three diosgenyl saponins isolated from Paris polyphylla have been reported to have immunostimulant properties.Lymphocyte stimulation tests were performed on eight cycloartane-type saponins isolated from Astragalus melanophrurius, to

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determine the role of saponins in the immunomodulating effect of the plant. Higher concentrations of tested compounds have exhibited inhibitory effects. Cycloartane and oleanane-type triterpenes from these species have unmistakably induced interleukin-2 activity.

From the above review it should be evident that there are many medicinal plants which exert immunomodulatory activity in experimental models at a particular dose. Different types of screening methods both in vivo and in vitro have been employed to determine their pharmacological activity. Some medicinal plants may stimulate the immune system, (e.g., Panax ginseng, Ocimum sanctum, Tinospora cordifolia, and Terminalia arjuna), and some may suppress the immune response (Alternanthera tenella). Also, various secondary metabolites (e.g., alkaloids, glycosides, saponins, flavonoids, coumarins, and sterols) exhibit a wide range of immunomodulating activity. Thus a successful review has been achieved by our above survey.

Immunomodulatory effects of some traditional medicinal plants[1]

The Asteraceae family is the largest flowering plants having immunomodulatory activity. This family consists of about 900 genera and some 13,000 species. Different plants having immunomodulatory activity are.

Boerhaavia diffussa

Boerhaavia diffusa, (Punarnava; Family Nyctaginaceae), is a creeping weed found abundantly all over India. In Indian traditional medicine, roots of this weed are used for the treatment of dyspepsia, jaundice, enlargement of spleen, abdominal pain and as an antistres agent.

Curcuma longa

Curcumin is a main active constituent of *curcuma longa linn* belonging to the family of Zingiberaceae. India is a largest country which produces the *curcuma longa linn* (about 90% of the total output of the world). Curcuma is a genus of about 70 species if rhizomatous herbs distributed in south East Asia especially India, China, Thailand and Malaysia. The curcumin is used for the treatment of anti-inflammatory, antiarthritic, common colds & coughs, jaundice agent. Curcumin also inhibited the IL-2 induced proliferation of splenic cells. The inhibition of IL-2 induced proliferation of cells was dose-dependent;

Rhododendron spiciferum

The plant *Rhododendron spiciferum* belonging to the family Ericaceae. They will be widely used as a medicinal plant because of their active constituent's proanthocyanidin A-1 (PAA-1) is highly used for health. Proanthocyanidin A-1 (PPA-1) is used as the free radical scavengers, anti-bacterial agents and effective enzyme inhibitors. They also exhibit the activity of vasodilators, anti-allergic, anti-inflammatory, cardio-protective, immune-stimulating, antiviral and estrogenic activities.

Caesalpinia bonducella

Caesalpinia bonducella belonging to the family Caesalpiniaceae. It is commonly known as Nata Karanja. It is indigenous plant of India but also found to be Myanmar, Sri Lanka. The Caesalpinia prickly shrub, globular shaped seeds with a smooth shining surface. The Seeds of these plants consist of a thick, brittle shell with a yellowish white bitter fatty kernel. *Caesalpini bonducella is used the* shows following therapeutic activity like antipyretic, antidiuretic, anthelmintic and antibacterial, anti-anaphylactic and antidiarrheal, antiviral, antiasthmatic, antiamoebic and anti-estrogenic. In the treatment of liver disorder and tumor, *Caesalpinia bonducella* has been traditionally used.

Tinospora cordifolia

Tinospora cordifolia belonging to the family of Menispermaceae. This is a perennial climber distributed throughout the tropical Indian subcontinent. It is categorized as in Ayurveda and well known for its adaptogenic and immunomodulatory activity in fighting infection. The activity of this drug appears to be due to alkaloid. The drug shows immunomodulatory activity. It is shown to be effective against various types of experimental induce infection.

Nelumbo nucifera

Nelumbo nucifera is a plant belonging to the family of Nymphaeaceae. This plant is a well-known aquatic medicinal plant which has used as a traditional medicine in India. The rhizome extract of Nelumbo nucifera, is used the activity of hypoglycaemic, antidiarrhoeal, antimicrobial, diuretic, antipyretic, psychopharmacological, anti-inflammatory. The seed of this plant is also used for the following activity including anti-ischemic, antioxidant, hepatoprotective, antiproliferative, , anti-inflammatory. The plant contains betulinic acid and a steroidal pentacyclic triterpenoid .The each extract of this plant is used to the immunomodulatory activity.

Allium sativum

Allium sativum an important medicinal plant having immunomodulatory effects. Three proteins showing immunomodulatory were separated from garlic by Q-Sepharose chromatography of 30 kD ultrafiltrate of raw garlic extract. All these proteins exhibit the mitogenic activity towards human peripheral blood lymphocytes, murine splenocytes and thymocytes

CONCLUSION

From this review it was concluded that immunology is probably one of the most rapidly developing areas of medical biotechnology research and has great promises with regard to the prevention and treatment of a wide range of disorders, the inflammatory diseases of skin, gut, respiratory tract, joints and central organs. Immunomodulators are going to be a central part of medicine. Helping the body help itself by optimizing the immune system is of central importance in a society so stressed, unhealthily nourished and exposed to toxins that most of us are likely to have compromised immune systems. Immunomodulation, however, is a normalizing process, which correct weak immune systems and temper immune systems that are overactive, but they do not boost the immune system. Immunomodulators are becoming a viable adjunct to established modalities offering a novel approach for the treatment of infectious disease in the coming decades of 21st century. There are a number of natural agents (herbs) which are used for the enhancing of the body's response to disease. In recent time a large number of drugs extracted from the plants are coming in to the market by proper clinical trials. When taking any of these agents take proper advice on dose, length of treatment.

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Table 1. Classification of Immunosuppressants

Sr. No.	Mechanism of Action	Examples
1.	Inhibitors of Lymphocyte Gene Expression	Glucocorticoids
2.	Inhibitors of Lymphocyte Signaling	
	a) Calcineurin Inhibitors	Cyclosporine, Tacrolimus
	b) mTOR Inhibitors	Sirolimus, Everolimus
3.	Cytotoxic Agents	
	a) Antimetabolites	Azathiprine, Methotrexate
	b) Alkylating agents	
4.	Cytokine Inhibitors	
	a) TNF-α Inhibitors	Etanercept, Infliximab
	b) IL-1 Inhibitors	Anakinra
	c) IL-2 Inhibtors	Daclizumab, Basiliximab
5.	Antibodies Against Specific	
	Immune Cell Molecules	
	a) Polyclonal Antibodies	Antithymocyte Globulin
	b) Monoclonal Antibodies	Alemutuzmab
6.	Inhibitors of Immune Cell	
	Adhesion	Efalizumab
7.	Tolerogens or Inhibitors of	
	Immune Cell Costimulation	
8.	Miscellaneous	Immune Globulin

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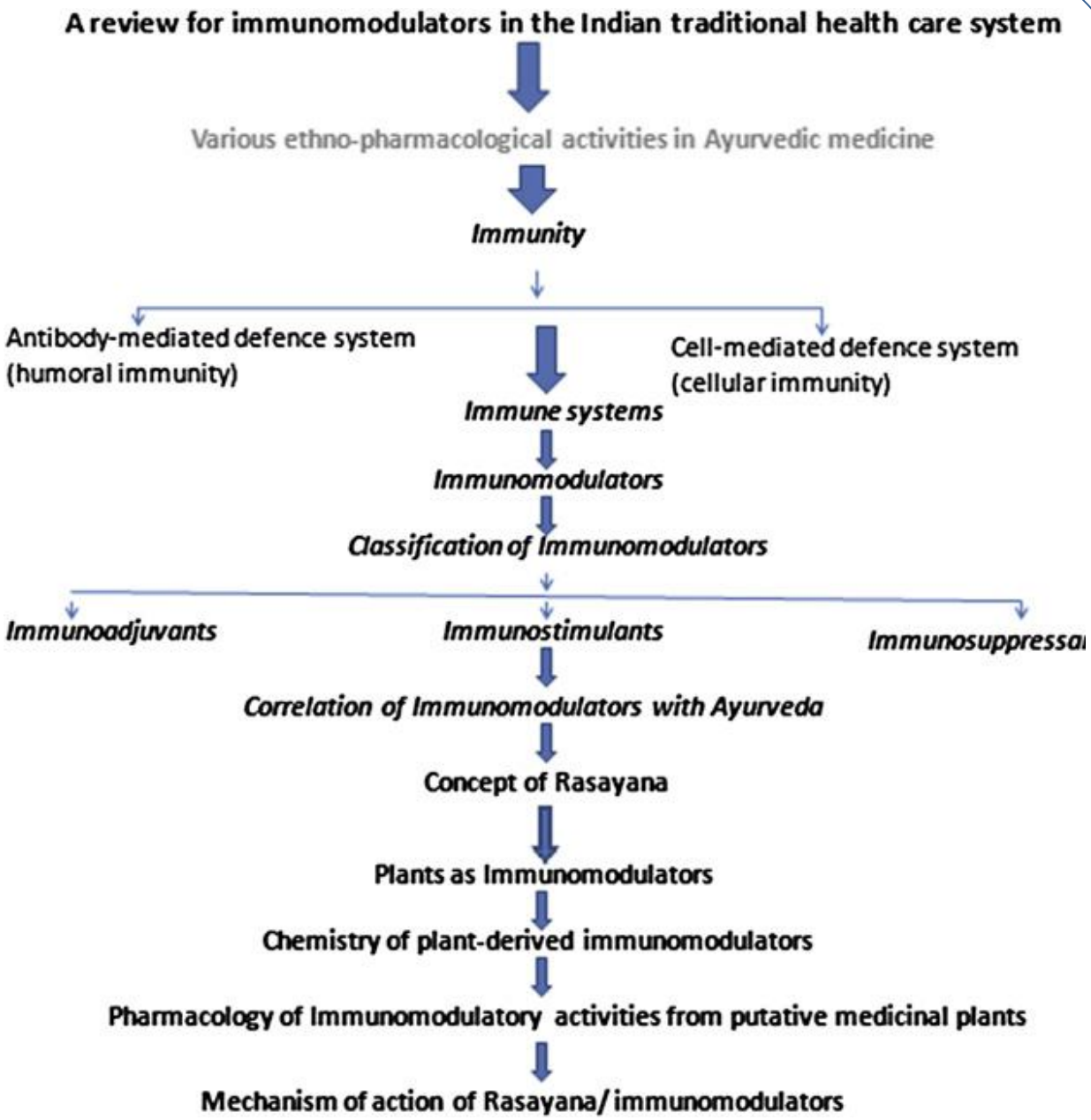

Figure 1. Review for Immunomodulators in the Indian Traditional Health care system

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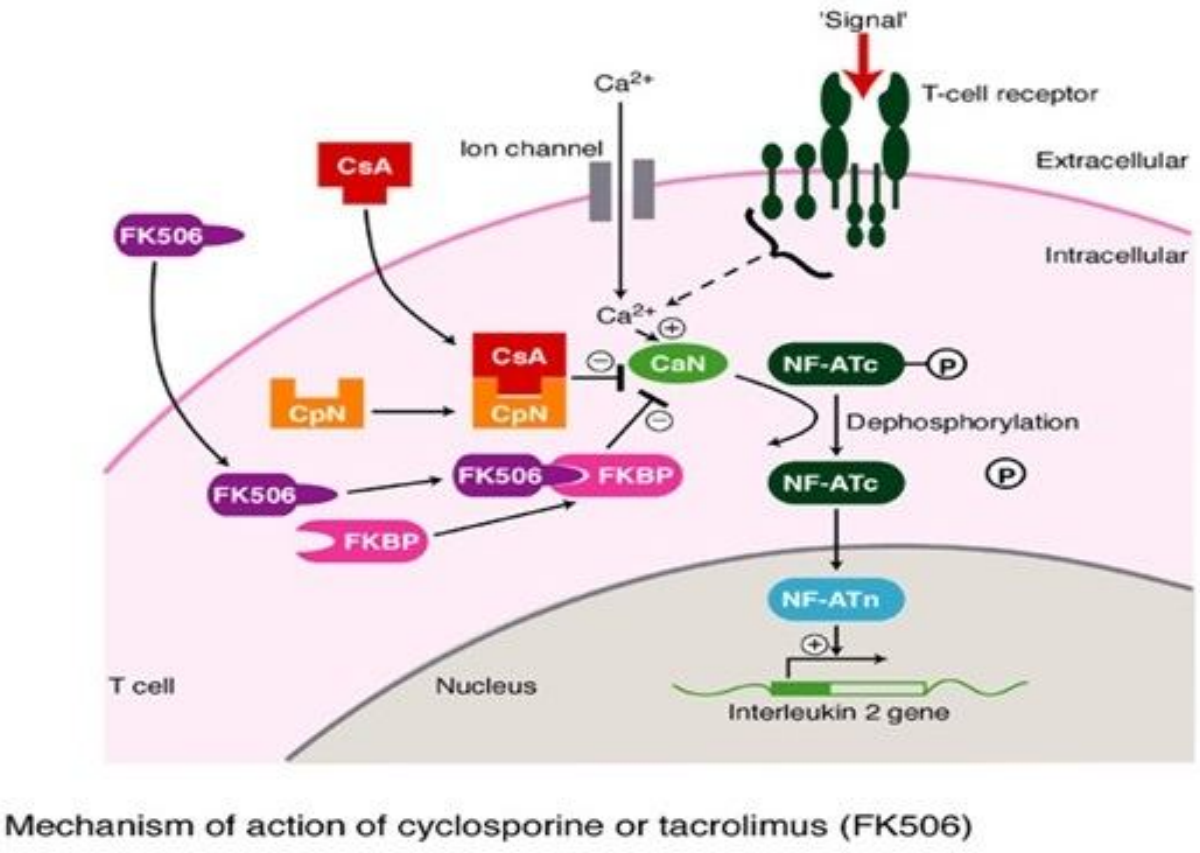

Figure 2. Mechanism of Action of cyclosporine

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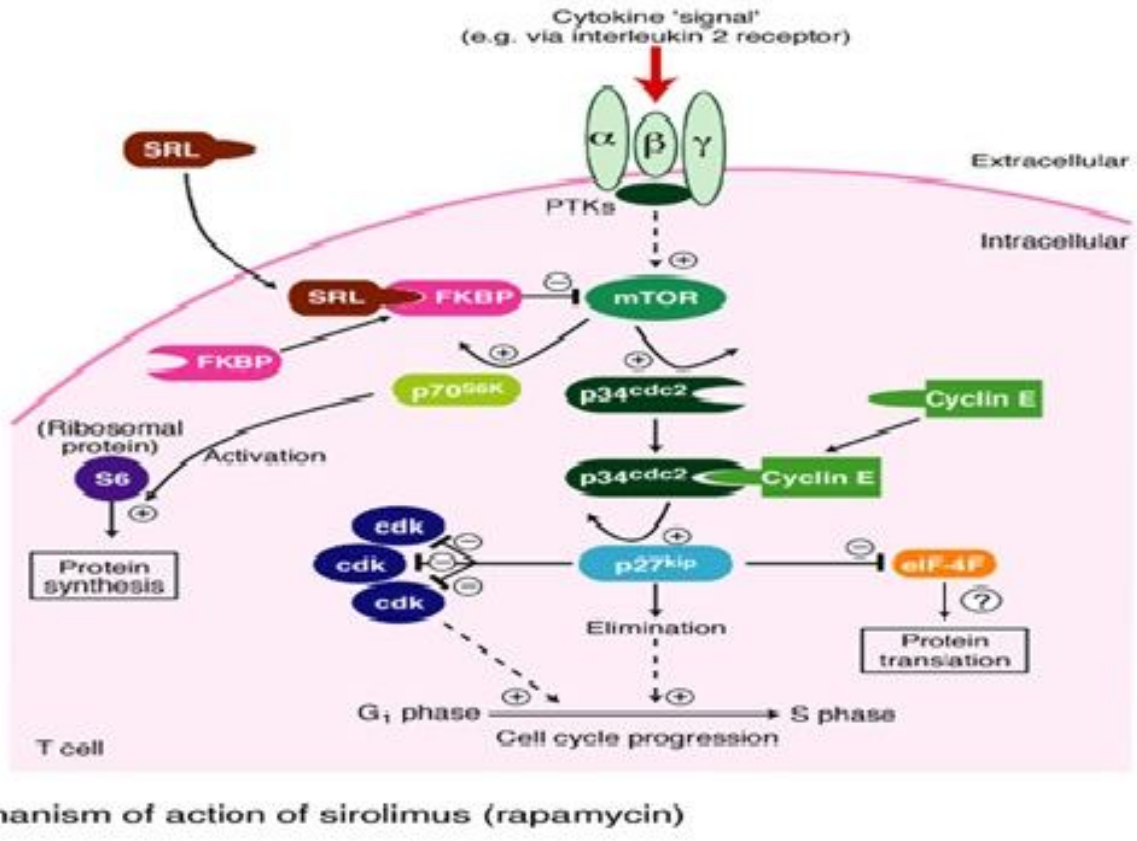

Figure 3. Mechanism of action of sirolimus