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EXPLORING IMMUNOMODULATION: PHYTOCONSTITUENTS AND MEDICINAL PLANTS IN IMMUNE SYSTEM ALTERATION

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ABSTRACT

The alteration of the immune response, which can either increase or decrease the immune responsiveness, is known as immunomodulation. Since ancient times, nearly every culture has relied on medicinal plants as a source of medicine to alter the immune system. The immunomodulatory properties of several medicinal plants have been investigated, and it has been found that animals' immune systems are altered through a variety of mechanisms. The phytoconstituents and medicinal plants used as immunomodulators will be discussed in detail in this review. This article highlights the types of immunomodulators, their mechanism of action, and their drugs including those on which the clinical trial is ongoing and the FDA approved as well as the patented drugs mentioned.

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INTRODUCTION

Immunity: The acquired immune system is characterized by immunological memory, although activation of the innate immune system can also improve susceptibility to subsequent infectious triggers. This is known as the immune system [1,2]. In addition, immunity distinguishes between the body's proteins and cells from foreign substances [3]. The immune response is the collective and coordinated response of specific cells and mediators against strange substances such as bacteria, viruses, etc once the foreign particle is identified. The immune system has been divided into two broad categories according to their function: the innate immune system, also known as the non-specific immune system, and the adaptive immune system, also known as the specific or acquired immune system [4].

Innate immunity: Although cytokines, acute phase proteins, macrophages, monocytes, and neutrophils are the primary mediators of the immune system that provide instant defense, innate immunity can also include physical, chemical, and microbiological barriers. Pathogen-associated molecular patterns (PAMPs), which are a collection of distinct moieties expressed by pathogens, are recognized by the host to indicate the presence of a pathogen. Antigen-presenting cells (APC) and macrophages play crucial roles in antibody-dependent cell-mediated cytotoxicity, cytokine secretion, NO production, antigen presentation, processing, and phagocytosis in all

Dendritic cells are the ones that activate naive and memory B cells as well as naive T cells. Natural killer (NK) cells, which by producing tumor necrosis factor (TNF), interferon (IFN), and granulocyte-macrophage colony-stimulating factor, regulate specific and natural immune responses during various phases of dendritic cell differentiation [5].

Adaptive immunity: The adaptive immune response is antigen-specific and includes immunity mediated by cells (such as T cells) and humoral cells (such as B cells), both of which are necessary for causing tissue inflammation or repair. Four distinct regulatory signals are involved in the T-cell response [6,7]. The specificity of the T cell response is determined by Signal 1 (antigen recognition). On antigen-presenting cells (APC), a major histocompatibility complex i.e. MHCI/II presents the antigen peptide, which interacts with antigen-specific T-cell receptors (TCRs) on naive T cells. The ligation of molecular pairs that are both stimulatory and inhibitory marks Signal 2 (the immune checkpoint) [6]. Immune cell activation is strengthened by Signal 3 (cytokine stimulation) [8,9]. Different cytokines that help T-cell clonal expansion and differentiation are made by activated APCs. A novel signal we proposed to describe small molecular metabolite-induced MADS is Signal 4 (MADS recognition) [10]. Recognition of MS. Antibody production by B cells is a characteristic feature of both innate and adaptive immunity [11]. T cell-dependent and independent B cell responses are the two types of B cell immunity. B2 cells mount antibody responses with the

cell response. The T-cell-dependent B-cell response is influenced by three signals. The specificity of the B cell response, in which the B cell receptor recognizes particular antigens, is determined by Signal 1 (antigen recognition). CD40/CD40L ligation features Signal 2 (immune checkpoints), which contributes to B cell activation, isotype switching, and affinity maturation. The B-cell immune response is strengthened by Signal 3 (cytokine stimulation). The innate defense of B1 cells against a wide variety of pathogen-associated molecular patterns/damage-associated molecular patterns (PAMP/DAMPs) is referred to as the T cell-independent B cell response. Natural IgM antibodies are secreted by B1 cells on their own in the absence of stimulation to maintain body resting immunoglobulin levels. To regulate both acute and chronic inflammatory conditions, B1 cells produce both natural antibodies and immunomodulatory molecules, such as IL-10, IL35, and granulocyte-macrophage colony-stimulating factors, in response to stimulation. Low affinity and polyreactivity distinguish B1 cell natural antibodies from B2 cell adaptive antibodies. There is evidence to suggest that B1 cell-produced IgM antibodies protect against atherosclerosis [12,13,14].

The body's macrophages are the first to recognize pathogens. In addition to chemokines, macrophages produce proinflammatory cytokines like IL-12 and TNF- when they interact with intracellular organisms like viruses and bacteria[15,16,17]. Natural killer cells, neutrophils, and T cells are drawn to the site of inflammation by these chemokines. Natural killer cells and macrophages secrete more IFN- as a result of the effects of IL-12 and TNF- on their activity[18,19]. In addition to enhancing macrophages' phagocytic and bactericidal capabilities, IFN- increases macrophage production of IL-12 and TNF-α [20,21]. Anti-inflammatory cytokines like interleukin-10 and 13 (IL-10, IL-13) and chemokines are produced by macrophages when they interact with extracellular parasites like fungi and worms [22,23]. IL-4 and IL-13 are produced by T lymphocytes, eosinophils, and basophils, which are drawn to these chemokines. Both IL-4 and IL-13 cause macrophages to produce more IL-10. IL-10 decreases the bactericidal capabilities of macrophages by reducing the production of proinflammatory cytokines [24], reactive oxygen species, and NO [25]. The innate immune response is developed during this step. The transformation of Th0 cells into Th1 cells is accelerated by the

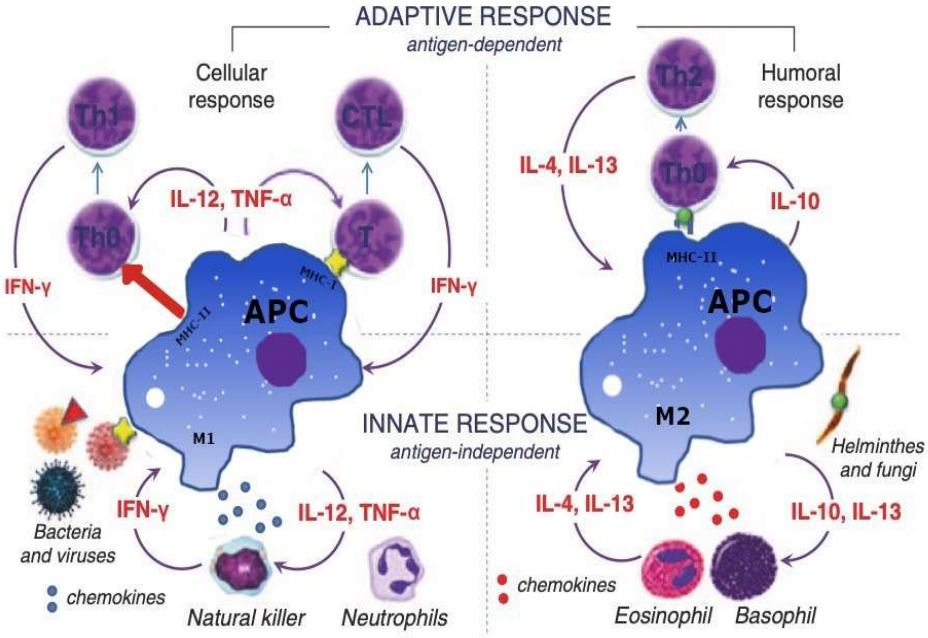

Fig. 1. The main steps of the development of innate and adaptive immunity

Table1. Difference between innate immunity and adaptive immunity [58].

Feature	Innate immunity	Adaptive immunity
Cells involved	Dendritic leukocytes, Natural killer cells, Mast cells, Granulocytes/ Macrophages, Basophils, etc.	Killer CD8+ T-cells, Helper CD4+ T-cells, B-cells, Antigen-presenting cells, etc.
Receptors	Germline encoded No somatic rearrangement Non-clonal distribution	Encoded in gene segments Somatic rearrangement necessary Clonal distribution
Molecules involved	Cytokines, Interferon, Acute phase reactants/ proteins	Antibodies, Cytokines
Response	Rapid (0-6 hours)	Days to weeks
Order of Defense	It is the first line of defense of the immune system	Action against pathogens that can evade or overcome an innate immune defense
Subsequent exposure	The immune response does not get altered on repeated exposure	Immune response get improves with subsequent exposure
Types of Immune response	Inflammation, Complement mediated killing, Phagocytosis	Antibodies generation, microbial destruction by Helper T cells and Cytotoxic T cells
Immunological memory	None	Confer
Allergy or hypersensitivity reaction	None	Immediate and delay
The reason behind immune evasion	Caused by pathogenic virulence	Caused by mutation of the recognized antigen
Potency	Low	High
Physioanatomicalcal barriers	Skin, Mucous membranes, chemicals, etc	Lymph nodes, mucosal-associated lymphoid tissue
Functions	• Bringing immune cells to the site of the infection; • Activating the complement cascade to identify antigens; • Identifying and removing foreign substances that are present in organs, tissues, blood, and lymph; • Activating the adaptive immune system through the presentation of antigens; • Providing a chemical and physical barrier against infectious	• The generation of responses that are tailored to maximally eliminate specific pathogens or infected cells • The development of immunological memory through memory B cells and memory T cells • The process of antigen presentation

antigens of intracellular microbes, the pro-inflammatory phenotype of macrophages, and the cytokines TNF-, IL-12, and IFN-. Th1 cells' response aids in the elimination of cancerous cells, viruses, and bacteria. The transformation of Th0 cells into Th2[26] cells is accelerated by the cytokines IL-10 and IL-4, the anti-inflammatory phenotype of macrophages, and the antigens of extracellular parasites. Extracellular bacteria, parasites, and toxins are neutralized by the humoral response of Th2.

Immunomodulator: For a long time, researchers have been interested in how different agents can change your immune system's response to a disease. Numerous exogenous and endogenous factors have an impact on the immune system's efficiency and function, resulting in either immunosuppression or immunostimulation. Immunomodulators are a group of substances that can normalize or modify pathophysiological processes. Immunological defense is influenced by endocrine and other immune system mechanisms, nonspecific and specific cellular and humoral immune responses, stimulation and suppression of immunocompetent cells, and other immune system mechanisms. The immunostimulants primarily target T, B, or the complement system. One important aspect of immunostimulation is for macrophages and granulocytes to perform more phagocytosis i.e. the process by which certain living cells called phagocytes ingest or engulf other cells or particles. For the activation of macrophages to take place it is probably necessary for the stimulating agents to remain in contact with the reactive cell. The second most important function is the stimulation of T lymphocytes, which can happen directly or through macrophages. The terms "immunomodulators," "immune restoratives," "immunaugmentors," and "biological response modifiers" refer to biomolecules of synthetic or biological origin that are capable of modulating, suppressing, or stimulating any aspect of innate or adaptive immunity. In clinical practice, immunomodulators are typically categorized as immunoadjuvants, immunostimulants, or immunosuppressants [27].

Immunostimulants: Immunostimulants are substances that act on or induce immune system mediators or components. A therapeutic or preventative strategy that aims to stimulate our nonspecific immune system is referred to as immunostimulation. Immunostimulants boost immunity against infections, allergies, cancer, and autoimmunity [28]. Because they are intended to improve a body's resistance to infection, immunostimulants are inherently nonspecific. Through innate and adaptive immune responses, they can act[29]. By increasing the fundamental level of an immune response, immunostimulants are anticipated to act as prophylactic and promoter agents in healthy individuals. They are anticipated to function as immunotherapeutic agents in patients with impaired immune responses[30]. This suggests primarily that natural killer (NK) cells, B-lymphocytes, monocytes, thymocytes, plasma cells, complement, granulocytes, T-lymphocytes, and macrophages are stimulated in a manner that is not dependent on the presence of an antigen**.** Fig.2. depicts the summary of the mechanism of action of immunostimulators.

Interferons, TNF-α and lipid analogues: Interferons are divided into three categories: alpha, beta, and gamma, which are produced by host cells in response to viral infections. Most of the time, they activate B lymphocytes that further activates plasma cell resulting in antibody production in the presence of antigen lipid A analogs and muramyl dipeptides [31]. Some common examples of drugs are interferon-β and Interferon-α-1b/2b.

Colony-stimulating factor: Colony-stimulating factors are glycoproteins that encourage the production of neutrophils in response to infection. These factors act through monocyte precursor which activates monocyte and macrophage which releases IFN-δ, M-CSF, IFN inducers, glycans lipid Aanalogs, muramyl dipeptide derivatives leading to activation and proliferation of T-cells (Fenichel et al., 1984). They are used in leukemia, AIDS, renal cell carcinoma, and hepatitis B and C. They make WBC, which is used to treat neutropenia caused by cancer, by activating stem cells in the bone marrow. For examplepegacaristim, romiplostim, etc.

NK cell mediator: Levamisole is the best example of an NK cell mediator that can increase neutrophil mobility, adherence, and chemotaxis, potentiate monocyte and macrophage function, enhance T cell responses by activating thymocyte and T-lymphocyte which further stimulates T cell activation and proliferation, and stimulate the formation of antibodies to various antigens. It also activates the NK cells which form IFNs and IFN inducers leading to cytotoxicity [32].

Interleukins: The cytokines known as interleukins, or ILs, are released by lymphocytes, monocytes, and macrophages and are released when they are needed. Through the proliferation of T- and B-cells and the activation of killer T cells, they control the immune system. They function as peptides that bind to helper T cell receptors and activate them when the antigen enters the body by attaching to macrophages. They cause the cell's PIP2 enzyme to be activated by their activation of the phospholipase C enzyme. It later on transformed into DAG and IP3 in further steps. IP3 further enhances calcium signaling, and calcium eventually binds to the calmodulin protein, activating the immune system dependent on calcineurin. Calcineurin may dephosphorylate T-cell nuclear factor attenuated (NFAT) protein[33]. The transcription process is enhanced when NFAT translocates and reaches the nucleus. It will result in the production of IL-2, which binds to helper T cell IL-2 receptors and promote T cell proliferation via the mTOR pathway. Aldesleukin and dupilumab are some common examples of interleukins. Fig.1. depicts the summary of the mechanism of action of interleukins.

Immunoglobulins (Rho D): These are IgG antibodies with a high titer of antibodies against the Rho (D)/Rh antigen on the surface of red blood cells. It works by neutralizing or preventing Rh-negative women from becoming sensitized. If the fetus is also Rh+ in the Rh - mother and the father is Rh +. Antibodies against Rh+ RBC are further produced and stored in the fetus's blood if it comes into contact with the mother's body. If the subsequent fetus is Rh+, the antibodies in the mother's body further travel through the placenta to the fetus, potentially resulting in hemolytic syndrome in the infant [34,35].

Vaccines: There are a variety of vaccine types, including bacterial, viral, therapeutic, and combination vaccines. The immune system is stimulated by the presence of dead or attenuated bacteria in the bacterial vaccine. Antibodies that are produced in response to a specific strain of bacteria are immunized, preventing subsequent infections. The viruses in the viral vaccine are either attenuated or inactivated. The virus that has been killed or is dead has stopped reproducing, but it still contains more antigens and elicits a stronger immune response than live vaccines [36]. Vaccines that aim to stimulate the immune system to treat or cure disease are referred to as therapeutic vaccines. The antigens in the combination vaccine are combined to stop the same infection from spreading to multiple strains. Additionally, it has the potential to stop many diseases, including DPT, tetanus, diphtheria, and others [37].

Immunosuppressants: These are a group of drugs that are structurally and functionally different from one another. They are often given together to treat different kinds of organ transplant rejection and autoimmune diseases. Molecules that suppress the immune system are called immunosuppressants, and they can be used to control the pathological immune reaction that occurs after organ transplantation. In addition, infection-associated immunopathology, hypersensitivity reactions, and autoimmune diseases can be treated with these agents [38]. They work to obviate repudiation of transplanted organs and tissues, including the kidney, bone marrow, heart, and liver, among others, to avert graft-versus-host disease in bone marrow transplants, additionally kenned as the lymphocyte replication to host antigen and to treat conditions like myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis, psoriasis, and ulcerative colitis, all of which are thought to have a paramount autoimmune component in their pathogenesis. The majority of immunosuppressive medication regimens consist of two or more agents with distinct mechanisms of action that disrupt a variety of T-cell activation levels [39].

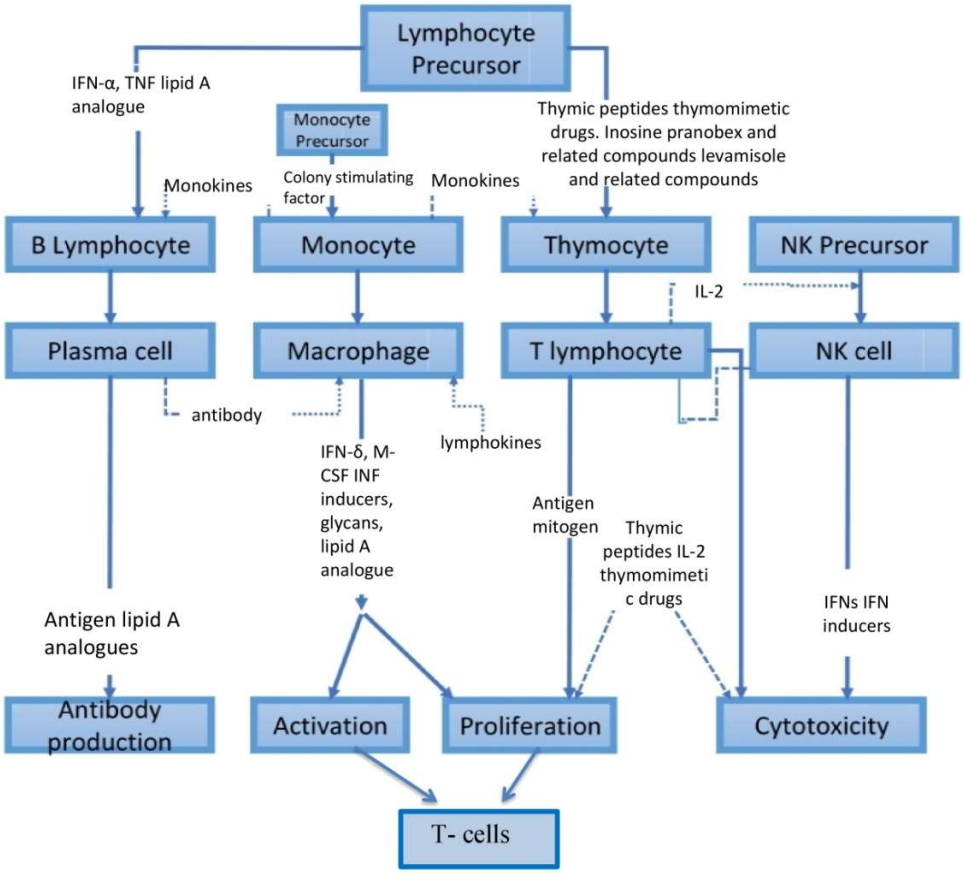

Fig. 2. Scheme depicting sites of action of various immunostimulants on pathways of the immune system

Mechanism of action: The co-receptor CD8 or CD4 binds to the MHC molecule, depending on the type of T cell. After that, the signal is transmitted through CD3, which is physically linked to the T cell receptor. However, a secondary signal is required because this initial signal is insufficient for T-cell activation[40]. When the CD28 receptor, which is found on T cells, binds the CD80 and CD86 molecules, which are found on antigen-presenting cells (APCs), a calcium-mediated signaling cascade is triggered. This secondary signal is also known as costimulation. The phosphatase calcineurin is an enzyme that dephosphorylates the nuclear factor of activated T cells (NFAT) and allows it to translocate from the cytoplasm into the nucleus in response to an increase in intracellular calcium levels. NFAT proteins and partnering transcription factors (TF) bind DNA target sequences inside the nucleus, activating genes that encode cytokines, including interleukin 2 (IL-2)—a major growth factor[41]. The newly produced IL-2 binds to the IL-2 receptors that are found on the surface of T cells, activating a signaling protein known as the mammalian target of rapamycin (mTOR). This allows the cell to move through the cell cycle and encourages the proliferation of antigen-primed T cells, which in turn produce more IL-2 and other pro-inflammatory cytokines that are responsible for activating natural killer cells, macrophages, and cytotoxic T cells. Fig. 3. shows the diagrammatic representation of the mechanism of action of immunomodulators as well as immunosuppressants.

Calcineurin inhibitors: This category of drugs works by binding to immunophilins, proteins that are found inside cells. Immunophilins are major receptors for the immunosuppressive drugs tacrolimus and cyclosporine, respectively, and are made up of two protein families called cyclophilins and FK-binding proteins. The nuclear factor of activated T cells (NFAT) is prevented from moving to the nucleus by these complexes, which then bind to and inhibit calcineurin. This ultimately hinders the transcription of genes that encode interleukin-2, which is required for T cell activation [42,43,44].

Costimulation blockers: Belatacept and abatacept are members of this class of drugs because they prevent T cells from interacting with CD28 by binding specifically to CD80 and CD86 on antigen-presenting cells (APC). T-cell proliferation and IL-2 production are also reduced as a result of this, which prevents complete T-cell activation. Because it is made to bind to CD80 and CD86 more strongly than abatacept, belatacept is better at suppressing the immune system needed for transplant rejection [45,46].

mTOR inhibitors: This group includes everolimus and sirolimus, both of which work by binding to the same intercellular FK-binding protein as tacrolimus. However, rather than forming a complex with calcineurin, sirolimus, and everolimus subsequently bind to mTOR, thereby inhibiting its activity. Both of these drugs are also referred to as rapamycin. Both the cellular response to IL-2 and the progression of the cell cycle is ultimately inhibited [47,48].

Antimetabolites: Mycophenolate mofetil and azathioprine, which both have a unique but similar mechanism of action, are the two agents in this class that are used the most frequently. After being activated into 6-mercaptopurine, azathioprine is further metabolized into purine analogs that resemble the structure of a DNA building block. In turn, these false purines can disrupt the purine synthesis de novo pathway and become incorporated into DNA and RNA, stopping their synthesis and preventing cellular proliferation. Mycophenolate mofetil works by blocking the enzyme inosine monophosphate dehydrogenase (IMPDH), which is important for purine synthesis and makes guanosine nucleotides. DNA synthesis, which requires guanosine triphosphate (GTP), is prevented, and cell proliferation is slowed down as a result. Mycophenolate mofetil, on the other hand, is not incorporated into DNA and does not cause chromosome breaks like azathioprine [49,50].

Corticosteroids: Prednisone, prednisolone, and methylprednisolone are examples of medications that fall under this category.

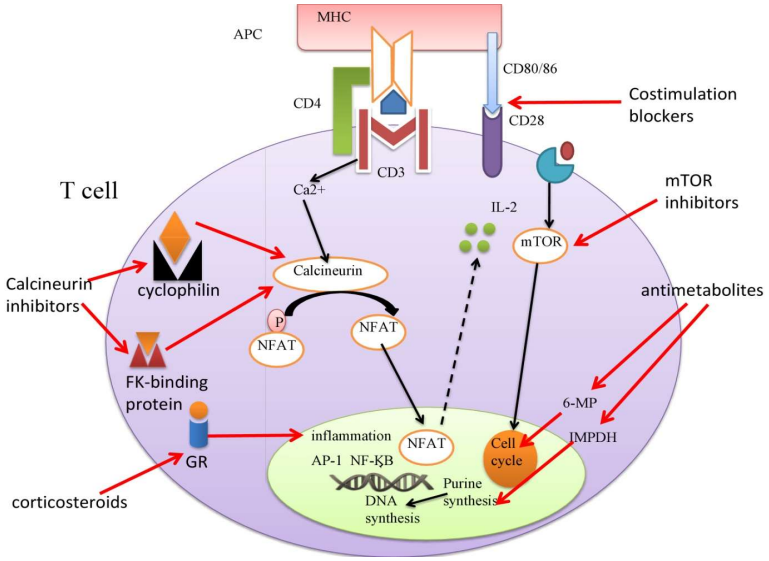

Fig. 3. Shows the diagrammatic representation of the mechanism of action of immunomodulators as well as immunosuppressants

Table 2. FDA approved drugs

Class	Drugs name	Year of approval	Uses
Traditional immunosuppressant[59]	hydroxychloroquine	1955	Psoriatic arthritis, Sjögren's disease
	Azathioprine	1968	Ulcerative colitis and Crohn's disease
	Leflunomide	1998	Allergies, Asthma, Eczema
	Methotrexate	1999	Cancer, Lupus , Rheumatoid arthritis (RA)
	Sulfasalazine	2000	Multiple sclerosis (MS), Psoriasis
	Cyclosporine	2000	Psoriatic arthritis, Sjögren's disease, Inflammatory bowel disease (IBD)
Biologics[60]	rituximab	1997	Ulcerative colitis and Crohn's disease
	infliximab	1998	Allergic conditions, Asthma
	etanercept	2003	Ulcerative colitis and Crohn's disease,
	omalizumab	2003	Inflammatory bowel disease
	ustekinumab	2009	inflammatory bowel disease (IBD), including ulcerative colitis and Crohn's disease
	tocilizumab	2010	psoriatic arthritis, Sjögren's disease,
	mepolizumab	2015	psoriatic arthritis, Sjögren's disease,
	secukinumab	2015	Asthma, eczema, infections
	dupilumab	2016	Atopic dermatitis
	abatacept	2021	ulcerative colitis and Crohn's disease
Disease-modifying therapy for MS [61]	interferon-beta 1a	1993	Inflammation
	interferon-beta 1b	1993	Inflammation
	glatiramer acetate	1996	psoriatic arthritis, Sjögren's disease, inflammatory bowel disease (IBD)
	natalizumab	2004	inflammatory bowel disease, including ulcerative colitis and Crohn's disease,
	ofatumumab	2009	psoriatic arthritis, Sjögren's disease,
	fingolimod	2010	multiple sclerosis (MS), psoriasis,
	cladribine	2011	cancer, lupus, rheumatoid arthritis (RA),
	ocrelizumab	2017	allergic conditions, including allergies, asthma, eczema, infections
	siponimod	2019	inflammatory bowel disease (IBD), including ulcerative colitis and Crohn's disease
Corticosteroids [62]	dexamethasone	1958	Infections, cancers such as leukemia, lymphoma,and multiple myeloma
	hydrocortisone	1998	IBD, allergic conditions
	prednisolone	2012	COPD exacerbations
	Prednisone	2012	Autoimmune disorders
Immunostimulants[63]	Provenge	2010	Asymptomatic or minimally symptomatic metastatic hormone-refractory prostate cancer
	Sipuleucel-T	2010	Asymptomatic or minimally symptomatic metastatic hormone-refractory prostate cancer
	Remune	2014	Asymptomatic or minimally symptomatic metastatic hormone-refractory prostate cancer

Corticosteroids have a wide range of effects that are likely controlled by many mechanisms. The regulation of T-cell responses is one mechanism by which corticosteroids cause immunosuppression [51]. Corticosteroids mediate their effects on T cells by binding to the intracellular glucocorticoid receptor [52]. This causes the complex to move to the nucleus and prevents key transcription factors like nuclear factor-kB and activator protein-1 (AP-1), which in turn alters gene transcription and represses genes that promote inflammation

Corticosteroids also have non-genomic effects by rapidly dissociating protein complexes associated with T cells and disrupting receptor signaling and T cell activation [54,55].

Antibiotics: Antithymocyte globulin consists of polyclonal antibodies that bind to a wide variety of proteins on the surface of T cells leading to cell death via complement-mediated cytotoxicity or apoptosis. Another antibody product commonly used in transplant is

Table 3. Contains the immunomodulators having clinical trials

Drug	Indication	Clinical trial number	Phase	Year
Nivolumab (monoclonal antibodies)	Deficiency mismatch repair (dMMR) or MSI-H metastatic colorectal cancer(67)	NCT02060188	II	2017
	Melanoma(68)	NCT01721746	III	2015
	Metastatic squamous Non-small-cell lung carcinoma (NSCLC)(69)	NCT01673867	III	2021
	Metastatic non-squamousNSCLC(70)	NCT01673867	III	2021
	Locally advanced or metastatic urothelial carcinoma (UC)(71)	NCT02387996	II	2021
	Advanced Renal cell carcinoma(72)	NCT01668784	III	2021
	Hematologic malignancy(73)	NCT01592370 NCT02181738	I ; II	2022
	Advanced hepatocellular Carcinoma(74)	NCT01658878	I&II	2022
	Recurrent/Metastatic Head and neck squamous cell carcinoma (HNSCC)[74]	NCT02105636	III	2021
Pembrolizumab(monoclonal antibodies)	Advanced or unresectable melanoma[75]	NCT01295827	I	2018
	Advanced or metastatic PD-L1-positive NSCLC[76]	NCT01295827	I	2018
	Locally advanced or metastatic UC[77]	NCT02335424 NCT02256436	II & III	2021,2022
	Recurrent or metastatic HNSCC[78]	NCT01848834	Ib	2019
	Hematologic malignancy[79]	NCT02181738	II	2020
	Microsatellite instability or mismatch repair deficient cancers[80]	NCT01876511	II	2021
	Advanced gastroesophageal Cancer[81]	NCT02335411	II	2019
	Metastatic Cervical Cancer[82]	NCT02628067	II	2022
	Locally advanced or metastatic, esophagus squamous cell carcinoma (ESCC)[83]	NCT02559687, NCT02564263	II	2021,2022
Cemiplimab (immune checkpoint inhibitor)	Advanced cutaneous squamous cell carcinoma (CSCC)[84]	NCT02383212, NCT02760498	I &II	2019,2023
Camrelizumab(monoclonal antibodies)	Classical Hodgkin lymphoma (cHL)[85]	CTR20170500/NCT03155425/ SHR-1210-II-204	II	2020
Toripalimab	Malignant melanoma[86]	NCT03013101	II	2021
Avelumab (PD-1 inhibitor)	Locally advanced or metastatic UC[87]	NCT01772004	II	2019
	Metastatic Merkel cell carcinoma[88]	NCT02155647	II	2022
Atezolizumab (monoclonal antibodies)	Previously treated metastatic NSCLC[89]	NCT01903993 NCT02008227	II & III	2018,2019
	Locally advanced and metastatic UC[90]	NCT02108652	II	2023
Durvalumab (monoclonal antibodies)	Locally advanced, unresectable NSCLC[91]	NCT02125461	III	2023
	Locally advanced or metastatic UC	NCT01693562	I & II	2020
Olopatadine(mast cell stabilizer)	Allergic conjunctivitis[92]	NCT01037179	III	2010
Fluticasone furoate (corticosteroid)	Allergic conjunctivitis to tree pollen or grass pollen[93]	NCT00891436	IV	2009
Modified allergen extract	Allergic rhinitis and conjunctivitis[93]	NCT01012752	III	2017
Sublingual immunotherapy	Seasonal rhinitis, rhinoconjunctivitis, and birch pollen allergy[93]	NCT00932607	II	2010
Biological: immunotherapy with modified extract of Olea europaea pollen	Allergy rhinoconjunctivitis[94]	NCT00831025	III	2013
Asparagine (human metabolite)	Red corpuscles encapsulating asparaginase[95]	NCT01523808 NCT02195180	I & II	2021
TNF-α (cytokines)	Adenoviral vector with hTNF-α linked to a radiation-induced promoter[96]	NCT00051467	III	2012
TNF-γ (cytokines)	Parvovirus and IFN-γ, improve the administration[97]	NCT02653313	I & II	2022
Selinexor (selective inhibitor of nuclear export)	XPO1/CRM1 inhibitor[98]	NCT02178436	II	2022
Masitinib (tyrosine kinase inhibitor)	c-kit, PDGFR, Lyn, and FGFR3[99]	NCT00789633	III	2018
Personalized medicine-bevacizumab (antiangiogenic agent)	Angiogenesis inhibitor[100]	NCT00260364	I & II	2016
Peptidomimetic of an NPC-1 epitope	MUC5AC[101]	NCT01834235	I & II	2019
Dendritic cells pulsed with peptides (GM-CSF, IFN-γ)	GM-CSF, IFN-γ, improving administration[102]	NCT02548169	I	2019
VEGFR2(anti-cancer)	Cancer vaccine targeting VEGFR2[103]	NCT01486329	I	2015

Table 4. Contains a list of patented immunomodulators

Publication name	Patent Number	Year	References
T. Peptide Related to Human Programmed Cell Death and DNA Encoding the Same	US5698520A	1997	[104]
Substance Specific to Human PD-1	US7563869B2	2009	[105]
B7-4 Polypeptides and Uses Therefor.	US7038013B2	2006	[106]
a Receptor for B7-4, and Uses	US7101550B2	2006	[107]
Methods and Compositions for the Treatment of Persistent Infections	US8652465B2	2014	[108]
Downmodulating an Immune Response With Multivalent Antibodies to PD-1	US6808710B1	2004	[109]
a Novel Immunoregulatory Molecule	US9062112B2	2015	[110]
B7-H1 Antibodies	US8981063B2	2015	[111]
B7-H1 and Methods of Diagnosis, Prognosis, and Treatment of Cancer	US7892540B2	2011	[112]
Method for Treatment of Cancer by Inhibiting the Immunosuppressive Signal Induced by PD-1	US7595048	2009	[113]
Antibodies to Human Programmed Death Receptor PD-1.	US8952136	2015	[114]
Anti-pd-l1 Antibodies and Uses Thereof.	US2014341917	2014	[115]
Anti-PD-L1 Antibodies, Compositions, and Articles of Manufacture	US8217149	2012	[116]
Targeted Binding Agents Against B7-H1.	US8779108	2014	[117]
Antibody Molecules to PD-1 and Uses Thereof.	US9683048B2	2017	[118]
Human Antibodies to PD-1.	US20150203579	2015	[119]
Pd-1 Antibody, Antigen-Binding Fragment Thereof, and Medical Application Thereof.	US20160376367A1	2019	[120]
Anti-PD1 Antibodies and Their Use as Therapeutics and Diagnostics.	US8735553B1	2014	[121]
Antibodies Directed Against Programmed Death-1 (PD-1).	US9815897B2	2017	[122]
Compositions of PD-1 Antagonists And Methods of Use.	US8609089B2	2013	[123]
Anti-pd-1 Antibodies and Therapeutic Uses Thereof.	US20180346569A1	2018	[124]
Simultaneous Inhibition of pd-l1/pd-l2.	US20130017199	2013	[125]
Anti-pdl1 Antibodies, Activatable Anti-pdl1 Antibodies, and Methods of Use Thereof.	US20160311903A1	2013	[126]
Human Monoclonal Antibodies to Programmed Death Ligand 1 (PD-L1).	US7943743	2011	[127]
Single Domain Antibody and Derivative Proteins Thereof Against Programmed Death-Ligand (pdl1)	US20180327494A1	2011	[128]
Compounds Useful as Immunomodulators.	WO2015034820A1	2018	[129]
Compounds Useful as Immunomodulators.	WO2015160641A2	2015	[129]
1,3-Dihydroxy-Phenyl Derivatives Useful as Immunomodulators.	WO2018009505A1	2015	[130]
Compounds Useful as Immunomodulators.	WO2017066227A1	2018	[130]
Biaryl Compounds Useful as Immunomodulators.	WO2018044963A1	2017	[131]
Symmetric or Semi-Symmetric Compounds Useful as Immunomodulators.	WO2018026971A1	2018	[132]
Immune Checkpoint Inhibitors, Compositions, and Methods	WO2018045142A1	2018	[133]
Immunomodulator Compounds	WO2018005374A1	2018	[134]
Bromo Benzyl Ether Derivative, Preparation Method Therefor, and Pharmaceutical Composition and Uses	WO2017202275A1	2018	[135]
Benzyl Phenyl Ether Derivative, Preparation Method Therefor, and Pharmaceutical Composition and Uses	WO2017202273A1	2017	[135]
Phenylate Derivative, Preparation Method Therefor, and Pharmaceutical Composition and Uses	WO2017202276A1	2017	[135]
Aromatic Acetylene or Aromatic Ethylene Compound, Intermediate, Preparation Method, Pharmaceutical Composition, and Use	WO2018006795A1	2017	[136]
1,3,4-Oxadiazole and Thiadiazole Compounds as Immunomodulators	WO2016142852A1	2018	[137]
3-Substituted 1,3,4-Oxadiazole and Thiadiazole Compounds as Immunomodulators.	WO2016142894A1	2016	[138]
1,3,4-Oxadiazole and 1,3,4-Thiadiazole Derivatives as Immunomodulators	WO2015033301A1	2016	[139]
1,2,4-Oxadiazole Derivatives as Immunomodulators	WO2015033299A1	2015	[140]
3-Substituted-1,2,4-Oxadiazole and Thiadiazole Compounds as Immunomodulators	WO2016142886A2	2016	[140]
1,2,4-Oxadiazole and Thiadiazole Compounds as Immunomodulators	WO2016142833A1	2016	[140]
Cyclic Substituted-1,3,4-Oxadiazole and Thiadiazole Compounds as Immunomodulators	WO2018051255A1	2018	[140]
Cyclic Substituted-1,2,4-Oxadiazole Compounds as Immunomodulators	WO2018051254A1	2018	[141]
Heterocyclic Compounds as Immunomodulators	WO2017205464A1	2017	[142]
Quercetin	CN102319237	2012	[143]
Apo-9-fucoxantinone	US2015/0182487	2015	[142]
Polyenylpyrrole derivatives	US20150284355	2015	[142]
Creosol	US20150005390	2015	[143]
β- Hydroxybutyrate	WO2016123229	2016	[143]
Sulfonylurea compounds	WO2016131098	2016	[144]
Cyclic diarylboron derivatives	WO2017031161	2017	[145]
Diacerein and analogs	WO2017031161	2017	[144]
Use of lipid-conjugates in the treatment of conjunctivitis	US20100087397	2013	[145]
A composition for the treatment of conjunctivitis comprising chlorogenic acid and derivatives thereof	WO2009045054	2009	[146]
A composition comprising glucosamine and derivatives thereof and a method for treatment of conjunctivitis using the same	WO2008035922	2008	[147]
Agent for treatment of allergic eye disease	US20080306163	2008	[146]
Treating conjunctivitis by topically administering an epinastine solution to the conjunctiva	US20080009476	2008	[148]
Compositions comprising a toll-like receptor or coreceptor antagonists and methods for treating or controlling ocular allergies using same	WO2009089401	2009, 2010	[149]
Pyrimidine derivatives for the treatment of asthma, COPD, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, cancer, hepatitis B, hepatitis C, HIV, HPV, bacterial infections and dermatosis	WO2009067081	2009	[146]
RNAi-mediated inhibition of spleen tyrosine kinase-related inflammatory conditions	US20090324507	2009	[150]
RNAi-mediated inhibition of histamine receptor h1-related conditions	US20090274631	2009	[151]
Use of a combination of olopatadine and cilomilast to treat non-infectious rhinitis and allergic conjunctivitis	US20090182035	2009	[146]
Heterocyclic inhibitors of histamine receptors for the treatment of disease	US20100120741	2010	[152]
Bicyclic heteroaryl inhibitors of PDE4	US20100081646	2010	[153]
Aminopyrimidine inhibitors of histamine receptors for the treatment of disease	US20100063047	2010	[154]
Methods and ophthalmic devices used in the treatment of ocular allergies	US20090324691	2009	[155]
Ocular allergy treatments	US20080051385	2008	[146]
Method of treating ocular allergy	US7687539	2010	[146]
Method for treating allergic diseases	US20100022470	2010	[156]

receptors with similar affinity as IL-2 thereby effectively competing with IL-2 and subsequently inhibiting IL-2 driven T cell proliferation [56,57].

Importance of natural therapy: The chemoprotective and immunomodulatory properties of traditional therapy-used plant extracts are being investigated. Modifiers of biological replications are called immunomodulators. Ameliorate the host's competency to bulwark itself from the tumor as a result of its antitumor effects. They not only have a direct anti-proliferative effect on tumor cells but withal ameliorate the host's capacity to withstand damage from toxic chemicals that could be habituated to kill cancer [58]. When the host's bulwark mechanisms must be activated under the conditions of impaired immune responsiveness or when selective immunosuppression must be induced in a situation, such as inflammatory diseases, auto-immune disorders, and organ/bone marrow transplantation, immunomodulatory therapy may provide an alternative to conventional chemotherapy for a variety of diseased conditions. It has been suggested that several "Rasayana" and Indian medicinal plants have the facility to modify the immune system. Some of these plants are Withaniasomnifera, Tinosporacordifolia, and Mangiferaindica. These plants have shown their immunomodulatory effects by affecting lymphocyte proliferation, decreasing the level of nitric oxide synthase, and enhancing the immune system through some antioxidant enzymatic activities. A lot more is still to be explored and offer scope for further investigation [64].

Immunomodulatory plant pharmacology: Due to increasing awareness of the immune system's modulatory strategy in the fight against infectious disorders, particularly viral infections, medicinal plant properties have been the subject of extensive research in recent years[65]. Folk medicine already uses many plants to treat and prevent viral infections by either directly attacking the pathogen or stimulating the body's defenses in a variety of ways. Because high doses typically result in an immunological disorder and low doses typically become immunostimulatory, there is a significant need to comprehend the medical specialty profile, administration, and dosage of plant-based drugs. Last but not least, it is important to keep in mind that the majority of in vitro and in vivo models are either insufficient or not straightforward enough to guarantee that the same substance is frequently used as a drug. Polysaccharides, for example, are one of the phytoconstituents that are considered to be biological response modifiers. They have been shown to support a variety of immune responses, including complement activation, lymphocyte proliferation, and macrophage stimulation [66,67]. Phenolic's immunopharmacological activities are intricate and still poorly understood. The observations of in vivo study are not always accepted as true by the in-vitro study. Additionally, the effects of various flavonoids may be antagonistic; they may be immunostimulatory or immunological disorders in some instances. Numerous flavonoids have been shown to have an impact on the functioning of protein systems that are crucially involved in both the generation of inflammatory processes and the immunologic response, particularly when it comes to the transmission of cellular activation signals [57,58].

CONCLUSION AND FUTURE ASPECTS

The different types of immunomodulators and descriptions of the immune system, its types, and its mechanism of action are among the review's primary highlights. Human history demonstrates that natural pandemics or epidemic diseases have killed millions of people in a short duration. As the process of developing a drug or vaccine is always time-consuming, controlling or treating these diseases required a consequential duration. In light of all of these factors, it is crucial to protect the body's natural immune system as well as to understand our immune system and the methods for boosting the body's immunity with the help of immunity-boosting substances. A body of knowledge has developed that shows a consequential withdrawal from conventional pharmacology, categorically regarding the connection between immune pharmacodynamics and dosing schedules. When it comes to evaluating agents and indicatingwhen to utilize them, this knowledge is crucial. It is important to keep in mind that different drugs can interact significantly with one another and that multiple agents can target the same molecular pathway at different abilities.When utilizing and combining drugs in clinical practice, it is essential to conformto all of these mechanisms. Some of these medicinal plants' immunomodulatory properties have been studied. Consequently, this review will not only help the researchers in learning about natural and synthetic immunomodulators but even in learning about a variety of FDA-approved and patented immunomodulators, as well as those for which clinical trials are currently being conducted.

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