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Review articles

Immunomodulation via phytoactive compounds a promising therapy for future medical system

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ABSTRACT

A cardinal role is played by the benign immune system in our body in defending different types of infectious diseases as well as continuous surveillance of its elements actively remove malfunctioning cells that could be dangerous to the body if retained as such. The whole immune system is elegantly coordinated through complex pathways via thousands of proteins, chemicals, and other types of bioactive mediators. However, if any type of exaggeration or inappropriateness occurs in the elements of this system, it leads to several fatal disorders. Such disorders range from hypersensitive or allergic reactions to numerous derangements like loss of normal ability to differentiate non-self from self, resulting in immune actions against body own tissues and cells called auto-immune disorders. Various endogenous and exogenous factors termed immunomodulators interact with the elements of the immune system to bring about an amplification or suppression of an immune response and are thus incorporated in achieving a specific therapeutic goal. Currently, in use immunostimulants, immunoadjuvants, and immunosuppressants pose a great threat to normal cellular functions. It is thus the utmost need of the hour that current research should be much focused on the development of novel immunomodulating agents especially incorporating the strategies of nanotechnology. This review is aimed at providing some details on the currently used immunomodulators in modulating the immune responses as well as the need for the development of novel phytochemical-based immunomodulating agents. This review is a humble attempt to encourage the researchers to perform their research in this field.

Keywords: Phytoactive compounds; Immunomodulators; Cytokines; Immune system; T- helper cell.

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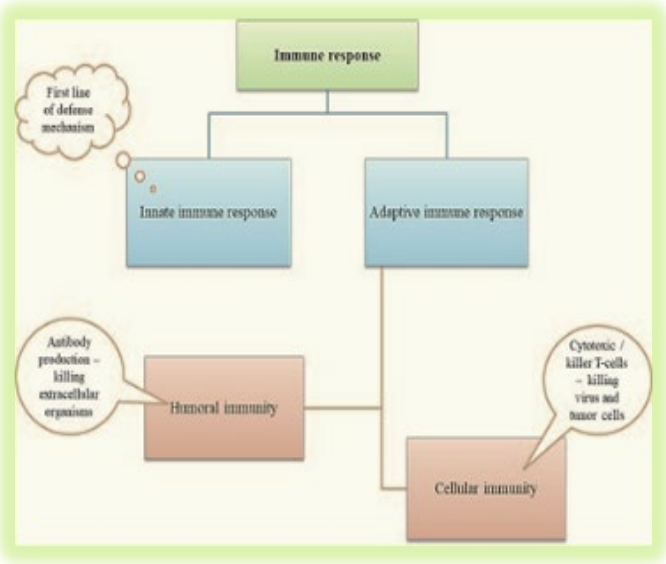
INTRODUCTION

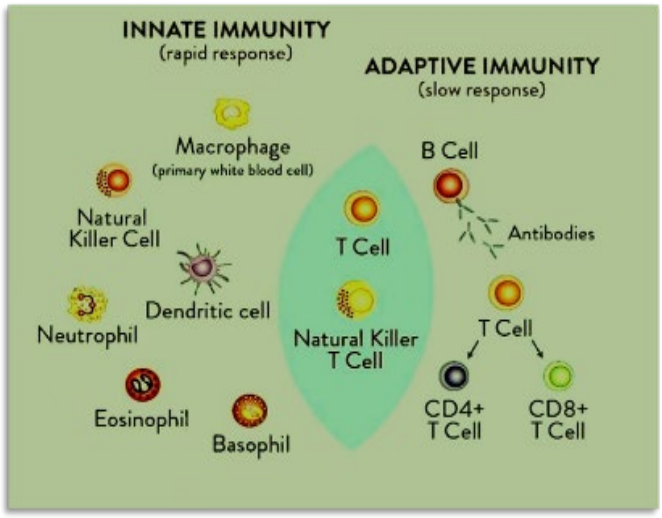
A eukaryotic organism's integrity is not only dependent on the exact expression of its genes but as well as on its liberty from pathogenic organisms that range from bacteria to parasites. There is competition of nutrients at cellular level when any of these pathogens invade a multicellular host. The organ system of the body that is constantly working to defend the body from invading microorganisms is the benign immune system without which a single prokaryotic cell would degrade the millions of interdependent cells of a multicellular organism. The immune system is a network of cells tissues and biological molecules that functions in a very complex but controlled manner to protect the multicellular body from infectious diseases as well as patrols the body to get rid of the malfunctioning cells that if retained as such may prove fatal for the body [1]. The science of immunology develops from medicine and serendipitous studies on the causes of immunity to disease. In today's day and age, immunology has become a vast field having its applications in numerous disciplines of medicine, particularly in the fields of organ trans-plantation, rheumatology, biologics development, oncology, bacteriology, virology, parasitology, dermatology, psychiatry [2].

Innate immune system (non-specific) and adaptive immune system (specific or acquired immune system) are two types of immune system (Fig.1). When a multicellular host is invaded by pathogenic bacteria, the innate arm of the immune system is the first to respond. The innate immune system is a complex network of sensory and response molecules that recognize and process antigens at the outset [3]. Pathogens produce a variety of conserved moieties known as microbe associated molecular patterns (MAMPs), which are identified by cells in the innate immune system's key actors. Evolutionarily conserved pattern recognition receptors (PRRs) abundantly present on phagocytes and antigen-presenting cells such as Macrophages, Dendritic cells, and Neutrophils recognize MAMPs. Binding of microbial conserved motifs known as Microbe associated

molecular patterns (MAMPs), such as LPS, lipoteichoic acid, Peptidoglycans, mannose-rich glycans, and host cell damageproducts.

Figure 1 (a) Figure 1 (b)
*(a & b): Types of immune response and different types of cells involved





Referred to as Damage-associated molecular patterns (DAMPs) to Pattern recognition receptors (PRRs), such as toll-like and NOD-like receptors, which are found on innate immune system cells (macrophages, dendritic cells, and neutrophils), prompt gene activation to code mediators and upregulate the immune system. The immune process in a controlled manner through secretion of different types of cytokines like interferon's, chemokines, tumor necrosis factors etc. [4]. These messenger proteins and peptides also play a cardinal role in the differentiation and activation of the cells of adaptive immune system. Adaptive immunity is acquired after antigens are presented to lymphocytes by antigen presenting cells and generation of specific Band T lymphocytes along with their memory retaining cells. Adaptive immunity develops in a week or month but remains throughout the life through development of antibodies and memory cells. Different antigens are neutralized and destructed after binding with antibodies, and this gives rise to humoral immunity. Another form of adaptive immunity is cell mediated immunity which is usually due to cytotoxic T lymphocytes that bring about direct lysis or apoptosis in the cells infected with intracellular pathogens like viruses [5]. Both the arms of immune system are coordinated through large number of bioactive mediators and cell surface receptors. Signaling pathways are regulated in a controlled manner in a normally functioning immune system. However, if any type of exaggeration occurs in the cells and molecules of this system, it proves fatal for the normal organ systems of the body. Such disorders range from hypersensitive or allergic reactions, inflammatory diseases, rheumatoid diseases to numerous derangements like loss of normal capabilityof differentiating non-self-cells and tissues fromself-ones, resulting in immune reactions against bodies own tissues and cells termed auto-immune disorders [6].

The member's ofPRRs families like NOD-like, mannose binding, RIG-I like, and toll-like receptors collectively termed Pattern Recognition Receptors (PRRs) that are abundantly present on phagocyteshave played a significant role in defense system. These receptors initially differentiate self from non-self in a coordinated immune response. Scientists from Batson to Tokyo have published a series of papers that give a clear image of how the elegant system of phagocyte cell Pattern Recognition Receptors (PRRs) that detect Microbe Associated Molecular Patterns (MAMPs) and Damage Associated Molecular Patterns (DAMPs) is disrupted when any kind of flaw in the signaling cascade occurs. Cytokines are the most important signaling molecules among them, as they signal and warn the entire immune system to recruit an army of cells and proteins to fight the foreign invader. Cytokines influence cell differentiation, the production of other cytokines, and the activation of specific cells. If, for example, more cytokines are generated following a signal than required for an appropriate immune response, this might result in a cytokine storm or cytokine toxicity, which in turn can lead to septic shock and trauma to normal bodily tissues [7, 8].

Immunomodulation

In healthy multicellular organisms, the immune system maintains homeostasis inside the body. In some immune system disorders, such as inflammatory disorders, autoimmune disorders, allergic disorders, and immunodeficiencies, however, it is necessary to modulate immune system components in order to induce, attenuate, amplify, or suppress the immune response in order to achieve therapeutic goals[9].As a result, immunomodulation (regulatory modification) is used as part of immunotherapy to prevent immune system exaggeration or dysfunction [9, 10].Effectors of both the innate and adaptive immunological arms are regulated from distinct differentiation phages of phagocytes, via inter-

regulated signaling processes that include other immune system components like the complement systemand other regulatory proteins. Complement pathways are important for connecting innate immune responses to the adaptive immune system, and immunomodulators have been found to act on complement activation pathways to bring about animmunomodulation. Any type of exaggeration or suppression in the pathways of this system is the main cause of immune system pathologies [10, 11]. Understanding these inter-connected immune system pathways in normal and malfunctioned forms are requisite for the development of novel immunomodulators.

Chemotherapeutic drugs or biologics such as monoclonal antibodies, processed cytokines, and other bioactive substances are commonly used in immunomodulation. These medications primarily target a certain signaling pathway in order to modify the immune response in a desirable manner. Drugs of this class, which are employed as immunostimulants, immunoadjuvants, and immunosuppressants, have a cytotoxic effect and have severe negative effects on the body's normal physiological functioning when utilized[11]. As a result, it is critical that research be conducted on innovative immunomodulators with fewer adverse effects. One of such opportunities to trace out novel immunomodulators is provided by plant based bioactive compounds. An ample amount of research had been carried out on the phytoactive agents that include flavonoids, polysaccharides, lactones, alkaloids, diterpenoids and glycosides. Such compounds have shown promising results as they have been revealed to possess potential to modulate immune responses without posing much harsh side effects.

When these phytoactive compounds are encapsulated in nanocarriers and delivered site specifically, their action seems to amplify to a great extent. Loaded nanocarriers are perfectly absorbed at the desired site and thus eschew the off-target and unwanted side effects. Plant based bioactive compounds coupled with nanotechnology has opened new routes in the field of therapeutics and current research should be focused on that very field. Thus, novel immunomodulators of plant origin can be formulated using the novel strategies of nanobiotechnology coupled with pharmacognosy [12].

People have relied on various plant-based formulations to treat a variety of ailments for a long time. Phytochemicals, which are naturally occurring active compounds in plantsare chemically phenolic and polyphenolic compounds. These bioactive agents have been used to treat a variety of ailments and disorders since the dawn of time without tracing their exact functioning mechanisms. Current advanced pharmacognosy research is heavily focused on such substances, particularly in conjunction with nanotechnology. Phytochemicals and their derivatives are being explored extensively in attempt to give a safer treatment for cancer, cardiovascular disease, inflammatory disorders, and other diseases. With an increase in the number of patients suffering from immune system problems, it became necessary to explore for alternatives to the present standard of care, which is fatal chemotherapy. A large repertoireof plant chemicals is yet to be studied for their human health benefits and potential in the treatment of deadly autoimmune and other disorders [13].Now-a days this research area is gaining much interest.

Theconcept of immunomodulation is based on any changes in immune response, which includes stimulation, expression, proliferation, or suppression of any steps of immune response. The popularity of immunomodulators is now increasing throughout the world among researchers, as a large number of compounds extracted from herbs and plants have shown potential to alter the immune system signaling cascades in order to suppress the disease susceptibility and to recover from diseases[14].

The field of immunomodulation pharmacognosy is vast and a lot of phytochemicals are yet to be observed for their potential to be used as immunomodulators. There is thus a dire need to conduct research and clinical trials on novel phyto active agents so that use of these benign bioactive compounds alone or in combination with currently employed therapies can be alternate way to manage different refractory diseases and disorders of immune system as well as boost its performance in health and disease. It is also imperative to focus on the targeted delivery of such potent compounds so that their action can be amplified and off-target side effects eschewed. Nanobiotechnology is now-a-days opening routes for the development of novel nanocarrier systems for the delivery of bioactive compounds specifically inside the body [15].

Need for the development of novel immunomodulators

Various endogenous and exogenous factors interact with the elements of immune system to bring about an amplification or suppression of an immune responses. Such agents that have the potentialto normalize or modulate the patho-physiological process are designated as immunomodulators. These bioactive compounds mainly target the pathways to treat different immune system related disorders and a few other cancers (Figure 2). They give their service in many different ways including working on the immune system directly by turning up some proteins/mediators and turning down others. Such therapeutic molecules are either synthetic or biologically originated with the capability of modulating, suppressing and stimulating immune responses. According to their function immuno modulators are categorized as immuno adjuvants, immuno stimulants, and immuno suppressants. A wide range of bioactive compounds are used as immuno restoratives, immuno genetics, and immuno suppresses which all fall in the category of immunomodulators [16].

Immunoadjuvants are agents that enhances or modulates the immune response to a vaccine. The word "adjuvant" has been derived from the Latin wordadiuvare which means to aid. Such substances act to delay, accelerate, or enhance antigen-specific immune responses when administrated with specific vaccine antigens. Currently there are a lot of adjuvants in widespread use, including inorganic compounds like potassium alum, aluminum hydroxide, aluminum phosphate, and calcium phosphate hydroxide, some oils, bacteria derived products, virosomes [17].

Immunostimulants are the compounds with the capability to potentiate immune system mediators and its components to provide resistance against autoimmunity, cancer, allergy, and infection. Processed cytokines like interferons and Aldesleukins are used as immunostimulants. Immunosuppressants however are the inhibitors of immune system, applied to control the pathologicalimmunereactionfollowing organ transplantation or any autoimmune event. They are also used as anti-inflammatory, anti-proliferative, anti-rejection agents. Examples include corticosteroids (Dexamethasone), Cytotoxic drugs (Azathioprine), Immunophilin ligands (Tacrolimus), and monoclonal antibodies. All these agents are administrated to modulate the components of immune system in order to induce, attenuate, amplify, or suppress the immune response according to therapeutic goals. However, the currently used immunomodulators in clinical practice are not without harsh side effects [17, 18].

Currently used synthetic immuno suppressants have different working mechanisms. They act in various ways like through inhibiting lymphocyte gene expression, inhibiting lymphocyte signaling, posing immuno-cytotoxic effects, inhibiting the messengers of immune system called cytokines, posing alkylating effects, neutralizing specific immune cell molecules, and inhibiting intercellular adhesion molecules. Inhibitors of lymphocyte gene expression include almost all corticosteroids like Dexamethasone, Prednisolone, Methyl prednisolone etc. They work by delaying leukocyte extravasation and reducing pro-inflammatory cytokine expression. Inverse effects of their use in human beings include bone necrosis, reduction in bone density, osteopenia, Cushing syndrome, hypertension, depression, and growth retardation in children. Inhibitors of lymphocyte signaling agents include Cyclosporin, Tacrolimus, Sirolimus etc. cyclosporin restricts the antigen triggered signal transduction in T- lymphocytes as well as reduce the expression of lymphokines and anti-apoptotic proteins [19]. Tacrolimus inhibits T-cell activation by inhibition of Calcineurin. Sirolimus inhibit activation and proliferation of T-cells. Side effects of using inhibitors of lymphocyte signaling agents include hepatotoxicity, nephrotoxicity, hyperkalemia, gum hyperplasia, hypercholesterolemia, hyperuricemia, and also pose cancer risk [20]. Cytotoxic agents incorporated as immunosuppresses include Azathioprine, Mycophenolic acid (MPA), Sodium azathioprine. Azathioprine prevents *de novo* purine synthesis which results in inhibition of lymphocyte proliferation. Mycophenolate sodium and Mycophenolate mofetil prevents *de novo* guanine synthesis by inhibiting the enzyme inosine monophosphate dehydrogenase. Inverse effects of using cytotoxic immunosuppressants include leukopenia, thrombocytopenia, hepatotoxicity, neurotoxicity, GI toxicity, pancreatitis, and cancer among others. Alkylating drugs like cyclophosphamide, which are employed as immunomodulators, work by cross-linking the DNA double strands to impede protein synthesis and cell division. Side effects of administrating such agents include Pancytopenia, graft versus host disease syndrome, cardiac toxicity hemorrhagic cystitis, hepatotoxicity among others [21].

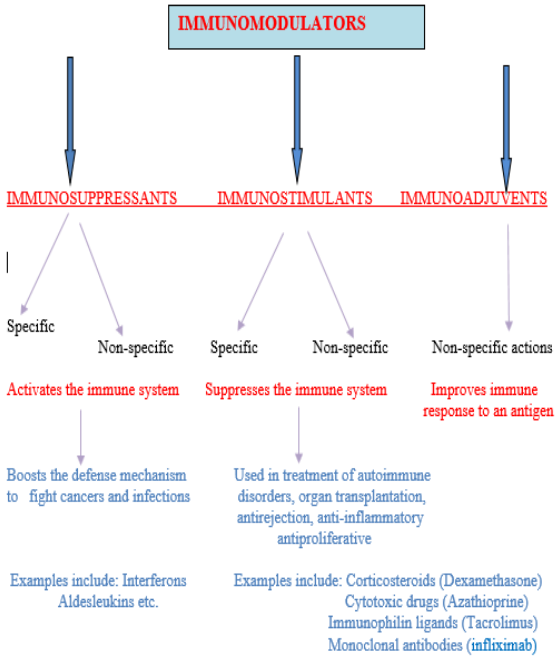
Monoclonal antibodies used as cytokine inhibitors include, infliximab, adalimumab, anakinra, daclizumab, basiliximab etc. These selective biologics bind with tumor necrosis factor alpha and inhibit it to bind with tumor necrosis alpha receptors via competitive inhibition. Inverse effects of using such agents include sepsis, hypersensitivity, anaphylaxis, psoriasis etc. other specific antibodies used against specific immune cell molecules to suppress immune response include proteins like anti-thymocyte globulin, muromonab etc. Anti-thymocyte globulins decrease circulating lymphocytes by inducing cytotoxicity in them as well as inhibit the functions of lymphocytes by binding with their cell surface markers that regulate the cell functions.

Muromonab prevents subsequent antigen recognition by internalizing the T cell receptors (TCRs). Fever, chills, cytokine release syndrome, myalgias, cardiovascular collapse, cardiac arrest, leukopenia, and thrombocytopenia are some fatal side effects posed by administrating these agents as therapeutics. Talizumab is the example of intracellular adhesion molecule inhibitors that are used as immunosuppressants. These agents inhibit T cell adhesion and trafficking by inhibition of LFA-1-ICAM interactions. Inhibition of such interactions *in vivo* can result in fatal bacterial infections, bacterial sepsis, viral meningitis, invasive fungal diseases, and multifocal leukoencephalopathy [20- 22].

Similarly, there are a lot of synthetic compounds as well as biologics that are used as immunostimulants. Best examples of such compounds include recombinant cytokines, hormonal analogs, imidazothiazole derivatives and other bioactive compounds. Recombinant cytokines like aldesleukin, interferon alpha and interferon gamma function by elevating immune cell activities such as enhanced phagocytosis and T cell lymphocyte cytotoxicity. Even using them as immunostimulants, such agents are not free from side

effects. For example, their use may lead to cardiomyopathy, hypotension, allergic disorders, arrhythmias etc. [23]. Imidazothiazole derivatives like Levamisole are used to repair the suppressed immune functions of monocytes, macrophages, and B & T lymphocytes. Their administration may induce allergic reactions, anaphylaxis, flu-like symptoms, GI toxicity etc. Hormonal analogs like Isoprinosine are used to increase the production of cytokines like IL-1, IL-2, and IL-γ. These agents also trigger lymphocyte proliferation. Administration of these agents may lead to cytokine toxicity, CNS depression, Nausea, hepatotoxicity, hyperuricemia among others [24].

Figure 2: Immunomodulators types and their action



Current research is still focused on biologics, biochemicals, and other synthetic compounds that can be incorporated specifically to target a single pathway of disease progression. It is however not possible to develop specific bioactive compounds that may have high selectivity and potency for a specific pathway, and low toxicity for off-target cells and tissues. Hence, the design and development of novel immuno-bioactive compounds from numerous conventional and alternative sources is the need of hour. The immunomodulatory properties of plant-based bioactive compounds are gaining much attention in current research. Herbs and plant extracts with their active moieties possessing immunomodulatory potential, may bestow us with novel entities to formulate new immunomodulatory agents to supplement the actions of presently used chemotherapies. An ample amount of research has been conducted on numerous plant-based immunomodulatory compounds and these bioactive compounds are undergoing clinical trials. Currently, the clinical potential of compounds that are being investigated for their immunomodulator characteristics include capsaicin, quercetin, epigallocatechin-3-gallate (EGCG), curcumin, resveratrol, colchicine as well as other secondary plant metabolites like glycosides, saponins, alkaloids, flavonoids, sterols, essential oils, steroids, and terpenoids [25].

Plants derive immunomodulatory agents with their mode faction

Some noteworthy plants compounds that have been revealed to possess immune system modulating properties are listed in Table 1. All these plants derived compounds have exhibited potent effects on both cellular and humoral immune functions in pre-clinical investigations. Several plant extracts are being used for their immuno modulatory effects. A list of some plants with immuno modulatory actions are summarized in the Table2.

Table 1: immune system modulating properties are listed in

Name of Compound	Plant source	Mode of action	Reference
Piperine	PiperlongumL.	Decrease level of pro inflammatory cytokines IL-1β, IL-6, and TNF-α.DecreaseCOX-2, NF-κBandNOS-2, expression. Enhance the amount of total WBC.	[25]
Berberine	Coptischinensis French.	Decrease theProduction of cytokines from T-helper cells [Th1 (IL-2), and Th2 (IL-4)].	[26]
Koumine	Gelsemium elegans (Gardner & Chapm) Benth.	Suppress proliferation of T lymphocyte.	[27]
Xanthohumol and Dihydro xanthohumol	Humuluslupulus L.	Block NO production that is induced By lipopolysaccharides (LPS) and interferon gamma (IFN-γ).	[28]
Echinocystic acid	Luffa cylindrica (L.)M. Roem.	Increasephagocyticabilityofmacrophages.	[29]
Gelselegine	Gelsemium elegans (Gardner &Chapm) Benth	Suppress proliferation of T lymphocyte.	[27]
Pseudocoptisine	Corydalisturts chaninovii Besser	InhibitERKandp38phosphorylation to suppress the activation of NF-κB, as a result reduce the level of pro–inflammatory mediators.	[30]
Sinomenine	Sinomeniumacutum (Thunb) Rehder & E.H.Wilson	Down regulateinflammatorycytokineproduction.Reduce VCAM-1 expression.	[31]
Z-ligustilide	Angelica sinensis (Oliv.) Diels	Reduce induction of COX-2 and iNOS via NF-k B regulation and signal Pathways of mitogen-activated protein kinase-1 (MAPK).	[32]
Sophocarpine	Sophoraalopecuroides L.	Decrease nitric oxide (NO) synthesis and pro-inflammatorycy tokines (TNF-αandIL-6) Production. Suppress synthesis of NOS and COX-2.	[33]
Leonurine	*Leonurusjaponicas* Houtt.	Suppress the activation of TNF-α, IL-6,I NOS, COX-2Andpromotetheactivationof IL-10 by suppress in g to L l like receptors synthesis and nuclear factor kappa B(NF-κ B)activation.	[34]
Butein	*Semecarpusanacardium*L.f., *Dalbergiaodorifera* T.C. Chen,	Attenuation of iNOS expression and thus suppress NO production. Block translocation of NF-κB.	[35]

	Toxicodendronvernicifluum (Stokes) F.A. Barkley		
Genistein	*Glycinemax* (L.) Merr.	Suppress iNOS andCOX-2expression.ReduceIL-1βandTNF-αproductionthroughactivationofperoxisomeproliferator-activatedreceptors(PPARs).	[36]
Nobiletin	*Citrusnobilis* Lour., *Citrusaurantium* L.	Suppressexpressionofpro-inflammatory mediator'siNOSand COX 2throughinhibitingtheNF-κBandsignalingpathway ofMAPK.	[37]
Luteolin	*Lonicera japonica* Thunb.	Decrease release ofINF-γ,IL-6,reduce expression of COX-2,ICAM-1. Suppress synthesisof heat shock protein90.	[38]
14-deoxyandrographolide,14-deoxy-11,12 didehydro andrographolide	*Androgra phispaniculata* (Burm.f.) Nees	Increase lymphocyteproliferation.ImproveinductionofIL-in lymphocytes.	[39]
Rutin	*Rutagraveolens*L.	Inhibit migration ofleukocyteInhibitproductionofTNF-αandIL-6.Block NFκB activation and extracellular regulated kinase.	[25,30]
Celastrol	*Tripterygiumwilfordii* Hook.f.	Block pro-inflammatorycytokinesexpression.	[28]

Table 2. Table of various plants with their immunomodulatory properties.

Plant Name	Immunomodulatory actions	Reference
Jatrophacurcas L.	Stimulate innate and adaptive immunity significantly via enhancement of antibody production. Enhance lymphocyte and macrophage cells count.	[40]
Glycyrrhizaglabra L.	Increase activities of antioxidant enzymes to stabilize immune cells.	[37]
Allium sativum L.	Enhance natural killer (NK) cell activity and proliferation	[22,36]
Plantago spp.	Enhance the secretion of IFN-ϒ.	[20, 41]
Ocimumtenuiflorum L.	Limit the release of antigen-induced histamine from peritoneal mast cells, as well as leucocyte migration.	[24,39]
Nigella sativa L.	Improve the function of natural killer (NK) cells by increasing the ratio of CD4 to CD8 T cells.IL-3 and IL-1 production is increased.	[17,36]
Morindacitrifolia L.	Increase release of TNF-α, IL-β, IL- 10, IL-12, IFN-ϒ, but inhibit the release of IL-4.	[9]
NelumbonuciferaGaertn.	Reduce NO generation, impede mast cell degranulation, and histamine release.CD40, CD80, and CD86 expression should be increases number of lymphocytes significantly.	[19]
Hippophaerhamnoides L.	Enhance IL-2 and IFN-ϒ production.Accelerate production of interleukin-6 and TNF-α in peripheral blood mononuclear cells (PBMCs). Suppress CD25 expression.	[35,39]
BoerhaaviadiffusaL.	Restrict human NK cell cytotoxicity in vitro.Blocks NO, IL-2 and TNF-α production.	[33]
Piper longum L.	Enhance total number of WBCs, bone marrow cellularity, and α-esterase positive cells.	[29, 35]
Calendula officinalis L.	Suppress tumor cell proliferation.	[25]
Tamarindus indica L.	Enhance phagocytosis, inhibits leukocyte margination.	[35,37]
Chelidoniummajus L.	Enhance proportion of CD4+, CD25+ regulatory T cells.	[32]
Urticadioica L.	Improve function of neutrophils.	[28, 19]
Glycyrrhizaglabra L.	Modulate NF-kB function and IL-10 production that reduce of inflammation in liver.	[18, 30]
Asparagus racemosusWilld	Enhance production of leucocytes.Increase phagocytic activity of macrophagesEnhance in antibody titer when injected as immunoadjuvant.	[27]
Carica papaya L.	Inhibition of growth of tumor cells.Reduce IL-2 and IL-4 production whereas enhance IL-12, IL- 12, IFN-gamma, and TNF-alpha without inhibition of growth in peripheral blood mononuclear cells (PBMC) of human.	[32]
Zingiber officinaleRosc.	Reduces the synthesis of IL-2 and IL-10, which inhibits lymphocyte proliferation.IL-1, IL-6, and TNF- production in activated macrophages should be increased.	[29,5]
Curcuma longa L.	T-cell proliferation, interleukin-2 production, NO production, and lipopolysaccharide-induced nuclear factor-kappa B (NF-kappa B) are all inhibited, and NK cell cytotoxicity is prolonged.Increase apoptosis by a significant amount.	[38]
BidenspilosaL.	Increase cytokine production and white blood cell population. Increase the activity of the IFN-promoter as well.	[26]
Centellaasiatica (L.) Urb.	Increase the total amount of WBCs in the body. Human peripheral blood mononuclear cells (PBMCs) proliferate more, and IL-2 and TNF- are released more.	[10, 33]
Terminalia chebula Retz.	Increases the overall antibody production.	[8]

CONCLUSION

Scientists from Batson to Tokyo have put forth a series of papers that reveal the detail of how the elegant innate immune system that detects Microbe Associated Molecular Patterns (MAMPs) and Damage Associated Molecular Patterns (DAMPs) by phagocyte cell Pattern Recognition Receptors (PRRs), complement cascade, as well as adaptive immune system pathways become disrupted when a flaw in the immune system's signaling cascades occurs. Immunological system modifying medications are either synthetic or biologically produced (cytokines, antibodies, etc.) and are mostly targeted on a specific target, with little efficacy in the treatment of many immunological disorders. Currently in use agents are not without deadly side effects. This necessitates the need for identifying novel chemicals as immunomodulators and using nanotechnological approaches to encapsulate them in nanocarrier systems so as to avoid off-target and undesirable systemic effects. Phytomedicines have been shown to pose less of a threat to the body's regular physiological functioning as compared to synthetic disease modifying agents. Researchers from several nations have

recently evaluated and investigated the chemical constituents found naturally in plants, as well as their mode of action, and it has been discovered that bioactive chemicals found in many plants can be used as immunomodulators. Novel nanotechnological approaches of encapsulating therapeutic agents inside nano system carriers are promising strategies to amplify their actions and eschew their off-target effects. These strategies are also providing opportunities to reconsider the compounds in treatment regimen that were once considered toxic. So, coupling the novel aspects of pharmacognosy with nanotechnology may prove promising in the development of bioactive compounds with accurate disease modifying potential. This review is an earnest attempt to inspire young researchers to pursue research in the said domain in order to develop new immunomodulating medications.

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