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Review Article

Plant-based Immunomodulators and Their Potential Therapeutic Actions

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Abstract

Immunomodulation is a diverse process by which immunomodulators enhance or suppress immune responses to control disease progression. Immunomodulators are a broad class of drugs that include immunosuppressants and immunostimulants. These agents have been used to fight against the dysregulated immune responses observed during tissue/organ transplantation and disorders, such as rheumatoid arthritis, ulcerative colitis, and cancers. Immunomodulators obtained from a myriad of plant sources are a major class of compounds that are known to have medicinal properties and are used for the treatment of various diseases. However, the mechanisms underlying the action of plant-derived compounds are poorly understood. Here, we discuss the major classes of plant-based immunomodulators with examples and their effects on the major signaling pathways, such as the nuclear factor kappa light chain enhancer of activated B cells (NF-κB), mitogen-activated protein kinase (MAPK), and mammalian target of rapamycin pathways. Importantly, we discuss the preclinical and clinical research to date to understand the importance of these immunomodulators. Overall, this review highlights the significance of plant-based immunomodulators as an alternative therapeutic strategy for combating various diseases.

Introduction

The immune system of the body is responsible for protecting it against infections, cancer, and other types of diseases. This highly evolved system is made up of innate and adaptive arms, each employing an intricate network of cellular and humoral entities to exert their function. However, dysregulation of the immune system due to various factors can cause excess autoreactive immune responses against the host, leading to autoimmunity,[1] or impair immune surveillance or deficiency in individuals, increasing their susceptibility to pathogens and cancers.[2] These dysregulated immune responses can be treated with natural and synthetic immunomodulators that are broadly classified as immunostimulators[3] or immunosuppressors[4] based on their ability to enhance or suppress immune responses, respectively (Fig. 1).

According to the National Stem Cell Foundation, the global autoimmune disease burden stands at 4% and encompasses greater than 80 distinct diseases. Furthermore, 1 in 1,200 people in the United States suffer with primary immunodeficiency diseases.[5] Given the range of immune-related disorders, there is a constant need for better and more potent immunomodulatory drugs to combat these disorders. Plant-based immunomodulators are one of the major classes of immunomodulators. Although beneficial, synthetic immunomodulators have the potential to cause many adverse side effects, ranging from skin rashes to systemic organ failures. These drugs can affect the nervous, respiratory, and digestive systems. For example, cyclosporine can cause side effects such as renal dysfunction and gum hyperplasia, while cyclophosphamide has cardiac toxicity.[6] These immunosuppressants may increase the risk of malignancies and teratogenicity. Additionally, the use of synthetic drugs for chronic diseases may face ineffectiveness, drug resistance, and high costs.[6,7] The synthetic immunomodulators may have a low selectivity and a

Keywords: Immunomodulators; Autoimmunity; Anti-inflammatory; T cell; Macrophage; Medicinal plants; Phytocompounds.

Abbreviations: COVID-19, coronavirus disease 2019; COX-2, cyclooxygenase-2; EGCG, epigallocatechin-3-gallate; ERK1/2, extracellular signal-regulated kinase 1/2; IκB, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor; ICAM-1, intercellular adhesion molecule 1; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa light chain enhancer of activated B cells; NO, nitric oxide; NOS2, nitric oxide synthase 2 (inducible); PGE2, prostaglandin E2; PI3K, phosphoinositide 3-kinase; PMA, phorbol 12-myristate 13-acetate; RA, rheumatoid arthritis; ROS, reactive oxygen species; STAT1, signal transducer and activator of transcription 1; Th1, type 1 helper T cells; Th17, T helper 17 cells; Th2, type 2 helper T cells; TNF-α, tissue necrosis factor alpha; TRPV1, transient receptor potential cation channel subfamily V member 1; VCAM, vascular cell adhesion protein..

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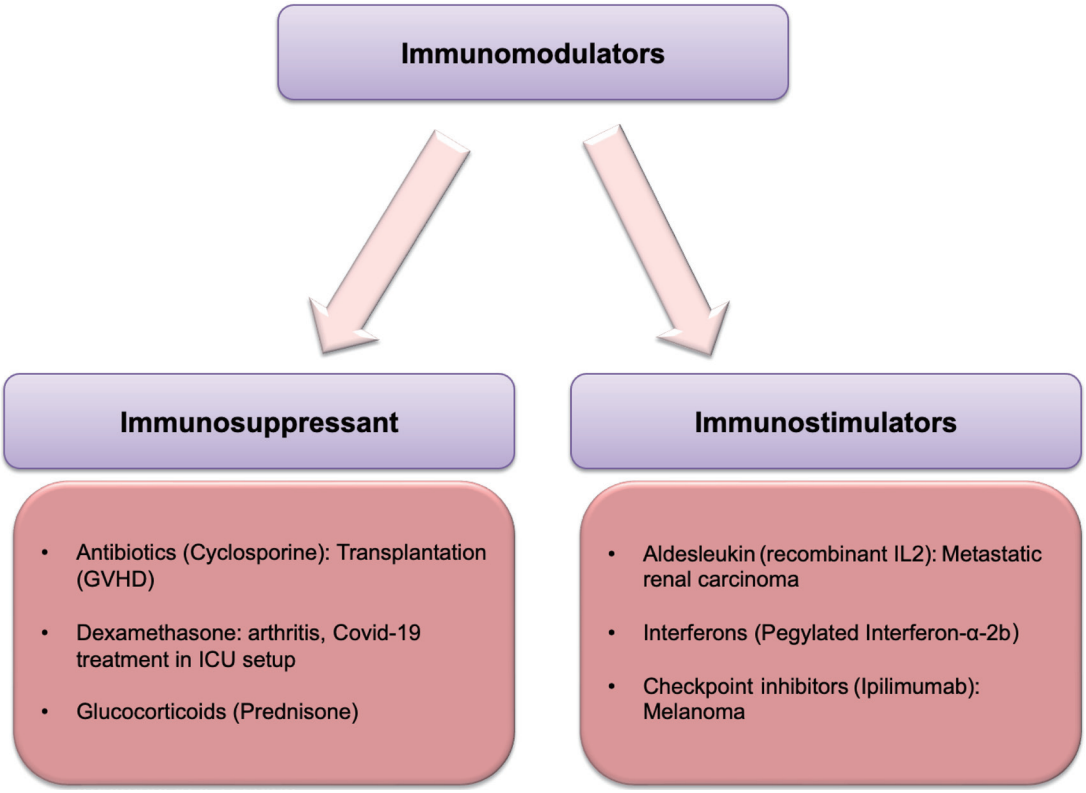

Fig. 1. Immunomodulators are a class of molecules that modulate different immune cell responses, thereby preventing life-threatening diseases. Immunomodulators can be classified generally into two broad classes: immunosuppressants, which suppress the immune responses and prevent various autoimmune disorders such as rheumatoid arthritis, inflammatory bowel disease and graft-versus-host disease (GVHD); and immunostimulants, which enhance immune responses to interferons and recombinant interleukin-2 (aldesleukin) that are required to combat disease conditions such as cancer. GVHD, graft-versus-host disease; ICU, Intensive Care Unit.

high toxicity.[6] Thus, it is imperative to uncover the therapeutic efficacy, safety, and potential mechanisms underlying the actions of plant-based immunomodulators as alternative therapeutic strategies for these dysregulated immune diseases.

Numerous herbal extracts and plant-based concoctions have been integral components of traditional medicine for many centuries. Two of the foremost types of ethnic medicinal practices that have stayed relevant across centuries belong to the Indian and Chinese cultures.[7] Traditional Indian and Chinese medicines have accounted for a number of plant species with distinctive beneficial functions against various diseases.[8] The pharmacological properties of these different plants include anticarcinogenic, anti-inflammatory, analgesic, and many others.[9] Plant-based immunomodulators are highly diverse and can be classified based on the chemical structures of the compounds, as mentioned in Figure 2 (adapted from PubChem), and the types of functions.

Here, we discuss the importance of the major classes of immunomodulators and their therapeutic effects in preclinical and clinical studies. Additionally, we highlight the pharmacological actions of these immunomodulators in regulating the major signaling pathways to elucidate their molecular mechanisms.

Therapeutic effects of plant-based immunomodulators

In recent years, the quest for alternative medicine has been fueled largely by safety concerns and economical options; therefore, it has catapulted natural compounds into the spotlight. Furthermore, plant immunomodulators that are extracted from abundant renewable sources and have low toxicity have increasingly yielded positive results in clinical trials.[10,11] This reinforces the therapeutic potential of plant-based compounds to modulate aberrant immune responses. Owing to the large-scale research conducted on bioactive phytochemicals, certain compounds have been exhaustively studied for their immunomodulatory roles.

Phytocompounds are broadly classified according to their molecular weights into high- and low-molecular-weight compounds. High-molecular-weight compounds are often primary metabolites required for plant growth and development and include glycoproteins, peptides, polysaccharides, and glycolipids.[9,12] On the other hand, low-molecular-weight compounds consist of alkaloids, phenolic compounds, quinones, terpenoids, saponins, phytoestrogen, and others.[9,12] These mostly overlap with secondary metabolites that themselves have been derived from primary metabolites. The major phytochemical groups and their components with immunomodulatory function are outlined in Table 1.[13–47] We focus on some plant-based immunomodulators that have been tested *in vivo* and even in clinical trials.

Curcumin

Curcumin is a naturally occurring diarylheptanoid molecule that can be obtained from the rhizome of *Curcuma longa*. This polyphenol

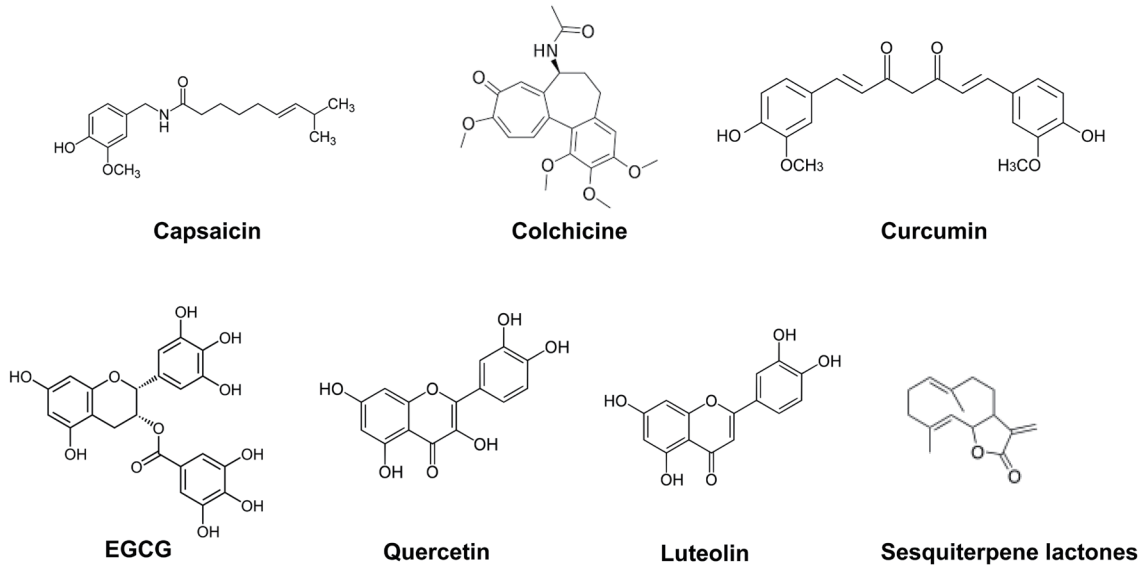

Fig. 2. Structures of key plant-based immunomodulators that have been demonstrated to inhibit major immune cell responses in both preclinical and clinical studies. The structures have been adapted from PubChem. EGCG: Epigallocatechin gallate.

has been extensively studied and is known for its diverse anti-inflammatory properties. Curcumin can downregulate the expression of proinflammatory factors, such as cyclooxygenase-2 (COX-2), nitric oxide (NO), tissue necrosis factor alpha (TNF-α), and interferon gamma (IFN-γ), in activated macrophages.[48,49] Curcumin inhibits nuclear factor kappa light chain enhancer of activated B cells (NF-κB) activation in phorbol 12-myristate 13-acetate (PMA)- and H_2O_2-stimulated human myelomonoblastic leukemia cells by preventing the phosphorylation and degradation of IκB-α.[50] Additionally, curcumin can block the binding of NF-κB to AP-1 in glioma cells.[51] Moreover, curcumin has been reported to affect the crosstalk between the NF-κB and Wnt/β-catenin pathways in cervical cancer cells.[52] More importantly, curcumin can be used as an adjunct therapy for maintaining the remission of ulcerative colitis in human patients,[53] and treatment with curcumin inhibits the proliferation of pathogenic T cells as well as reduces platelet hyper-responsiveness and neutrophil infiltration in a rat model of adjuvant-induced rheumatoid arthritis (RA).[54] Similarly, treatment with curcumin effectively downregulates the activation of the proinflammatory mammalian target of rapamycin pathway in synoviocytes and suppresses signal transducer and activator of transcription 1 (STAT1) signaling to reduce B cell activity in mice with collagen-induced arthritis as well as inhibits COX-2 expression and induces apoptosis in primary canine chondrocytes.[55] Furthermore, treatment with curcumin also decreases the expression of interleukin (IL)-1β, IL-6, IL-8, IL-17, IL-18, and TNF-α in animal models of RA.[55] In mouse models of experimental autoimmune encephalomyelitis, curcumin targets inflammatory monocytes and prevents their trans endothelial migration across the blood-brain barrier through inhibition of the NF-κB pathway as well as the expression of the cell adhesion molecules intercellular adhesion molecule 1 (ICAM-1) and macrophage-1 antigen.[56] Treatment with curcumin reduces the numbers of splenic T and B cells by downregulating the expression of NF-κB, AKT, and extracellular signal-regulated kinase (ERK) 1/2 and Bcl2 in rodents.[57] A balance between T cell subtypes is necessary not only for an optimal immune response but also for control of disease progression. Classically, aberrant type 1 helper T cell (Th1) responses contribute to the development of type 1 diabetes, while strong type 2 helper T cell (Th2) responses are crucial for the onset of asthma.[58,59] In some comorbid cases, the simultaneous existence of these antagonizing conditions may lead to an intermediate but distinct immune profile. In comorbid diabetic asthmatic murine models, oral treatment with curcumin reduces the levels of circulating IL-4 and eosinophils as well as mucus cell metaplasia and inflammation-induced nasal hyper-responsiveness in bronchoalveolar lavage fluid. Treatment with higher doses of curcumin also decreases the blood glucose levels.[60]

It is important to note that the immunomodulatory role of curcumin is dependent on its dose in tumor models. Unlike inflammatory diseases, neoplasms often rely on immune evasion for their unchecked growth and progression. Curcumin treatment may modulate immunosuppression through multiple actions.[61] Curcumin intervention can increase the effector T cell number and their activity by mitigating the NF-κB dysregulation in T cell tumor infiltrates to increase the susceptibility of tumor cells to TNF-α-mediated apoptosis. Furthermore, treatment with curcumin can attenuate regulatory T cell proliferation; IL-2, IL-10, and IL-6 production; M2 macrophage polarization; and natural killer T cell activation.[62] Previous studies have shown that curcumin treatment can effectively inhibit the growth of a wide range of cancers, including colon cancer, lung cancer, lymphoma, breast cancer, and others, in rodents and human patients.[63] However, curcumin treatment has the major disadvantage of a low bioavailability, which is now being investigated and enhanced by making chemical modifications to increase the potency of this molecule.[64] To increase the bioavailability of curcumin, a new modified compound known as nanocurcumin is being used in animal models such as chronic hypobaric hypoxia in rats.[65] More recently, nanocurcumin treatment in severe and mild coronavirus disease 2019 (COVID-19) patients has been demonstrated to ameliorate adverse inflammation by reducing T helper 17 cell (Th17) responses.[66]

Resveratrol

Resveratrol is chemically known as 5-[(*E*)-2-(4-hydroxyphenyl)

Table 1. List of major classes of plant-based immunomodulators with examples of each class and their roles in inhibiting various immune responses and thereby preventing diseases

Class	Source from which it is obtained	Mechanism of action
Alkaloids		
Lycorine	*Lycoris radiata*	Inhibits iNOS and COX-2 levels[15]
Piperine	*Piper longum* Linn	Inhibits proinflammatory cytokine production, NOS2, COX-2 production[16,17]
Tinosporin	*Tinospora cordifolia* (Willd.)	Antidiabetic, antihyperlipidemic, and antioxidant properties[18]
Essential oils		
Tetramethylpyrazine	*Ligusticum chuanxiong* Hort	Inhibits NOS2, IFN-γ, TNF-α, ROS, chemotaxis, *etc*. production in macrophages[19,20]
Z-ligustilide	*Angelica sinensis* (Oliv.) Diels	Inhibits MAPK and NF-κB and thus inhibits NOS2 and COX-2[21]
Chalcones		
Butein	*Dalbergia odorifera, Semecarpus anacardium* Linn, *Toxicodendron vernicifluum*	Blocks NOS2 expression and thus NO production, inhibits NF-κB translocation[22]
Licochalcone E	*Glycyrrhiza inflata*	Inhibits NF-κB- and activator protein-1-mediated IL-6, IL-1β, and TNF-α production[23]
Flavonols		
Rutin	*Ruta graveolens* L.	Suppresses leukocyte migration, reduces NF-κB activation, TNF-α, and IL-6 production[24]
Quercetin	*Dysosma veitchii* (Hemsl. et Wils)	Ameliorates the activity of NF-κB and NOS2, reduces cytokine production, and reduces VCAM-1, E-selectin[25–27]
Flavones		
Apigenin	*Cynodon dactylon, Salvia officinalis L., Portulaca oleracea, Mentha longifolia*	Reduces IL-1α and TNF-α levels with lower COX-2, NOS2, ICAM, and VCAM expression[28,29]
Luteolin	*Lonicera japonica*	Decreases in IFN-γ, IL-6, COX-2, and ICAM-1 levels[13,14]
Flavanols		
Epigallocatechin-3-gallate (EGCG)	*Camellia sinensis* L.	Reduces ROS, MAPK phosphorylation, adhesion protein expression, and STAT3 levels[30]
Isoflavones		
Genistein	*Glycine max*	Decreases NOS2 and COX-2 levels along with lower proinflammatory cytokine amounts[31]
Puerarin	*Pueraria lobata* (wild) Ohwi	Reduces NF-κB and STAT3 levels[32]
Quinones		
Shikonin	*Lithospermum erythrorhyzon* Sieb. Et Zucc.	Increases Th2 response and reduces Th1 via inhibition of NF-κB activity[33]
Thymoquinone	*Nigella sativa* L.	Blocks LPS-induced fibroblast proliferation. Inhibits an increase in IL-1β, matrix metalloproteinase-13, and COX-2 via blocking NF-κB and MAPK pathways[34]
Stilbenes		
Piceatannol	*Fallopia japonica*, nuts, *etc*.	Decreases NF-κB, NOS2, ERK, and STAT3 levels[35]
Resveratrol	*Fallopia japonica*, *Vitis vinifera* (grapes), *etc*.	Inhibits Th1 cytokine responses, MPO activity, and NOS2 and COX-2 expression[36]
Phloroglunicols		

(continued)

Table 1. *(continued)*

Class	Source from which it is obtained	Mechanism of action
Arzanol	*Helichrysum italicum*	Inhibits COX activity with reduced production of eicosanoids[37]
Myrtucommulone	*Myrtus communis* L.	Inhibits PGE2 production via inhibition of COX activity[38]
Saponins		
Diosgenin	*Dioscorea villosa, Trigonella foenum graecum*	Protects against neuroinflammation by inhibiting inflammatory mediators such as COX-2, NF-κBp65, and TNF-α.[39]
Panaxadiol	*Panax ginseng*	Enhances hematopoietic progenitor proliferation, T helper and regulatory T cell numbers while reducing the peripheral cytotoxic T cell population in a mouse model of aplastic anemia.[40]
Terpenoids		
Ginsan	*Panax ginseng*	Enhances cytokine production, ROS production, and macrophage phagocytic activity[41,42]
Triptolide	*Tripterygium wilfordii*	Blocks lymphocyte activation and expression of genes, causing reductions of IL-2, COX-2, and TNF-α levels[43]
Other Polyphenols		
Ellagic acid	*Fragaria* spp	Antioxidant and anticancer activity by regulation of STAT3, transforming growth factor-β/Smad3, *etc*.[44–46]
Others		
Apocynin	*Picrorhiza kurroa* Royle ex Benth, *Tripterygium wilfordii m* L. (Canadian hemp),	Suppresses NADPH oxidase activity with lower proinflammatory cytokine production. Also decreases both $CD4^+$ and $CD8^+$ production[47]

ICAM, intercellular adhesion molecule; IFN-γ, interferon gamma; LPS-induced, lipopolysaccharide; MPO, myeloperoxidase; TNF-α, tissue necrosis factor alpha; VCAM-1, vascular cell adhesion protein-1.

ethenyl] benzene-1,3-diol and is derived from stilbene and phytoalexin. Resveratrol is found in different dietary and plant products and is a major component of red wine and peanuts.[67] Resveratrol can regulate a number of inflammatory parameters in various immune cells: inhibition of NF-κB activation induced by lipopolysaccharide (LPS), PMA, and TNF-α in macrophages, Jurkat, myeloid, and epithelial (HeLa) cells through inhibition of IκB kinase.[68–71] It also downregulates COX-2 expression and NO levels in cytokine-stimulated human primary airway epithelial cells[72] as well as COX-2 expression in melanocytes by attenuating the ERK1/2 and PI3K/AKT pathways.[73] Moreover, resveratrol decreases the production of IL-12, IL-6, TNF-α, and others in lymphocytes and macrophages.[74,75] This molecule also inhibits the expression of adhesion molecules such as ICAM-1 on the surface of endothelial cells, thereby inhibiting cell recruitment.[76] The therapeutic effects of resveratrol in dysregulated immune disorders have been further studied in a range of animal models. Treatment with resveratrol can reduce lower airway inflammation and protect against infection-induced sepsis in mice and zebrafish as well as alleviate chronic obstructive pulmonary disease caused by nontypable *Haemophilus influenzae*.[77] In rat models of experimental arthritis and periodontitis, resveratrol treatment increases IL-4 expression in gingival tissue and decreases the levels of serum rheumatoid factor and anticitrullinated protein antibodies, thus emphasizing its anti-inflammatory effects.[78] Diabetic nephropathy is another dysregulated immune disorder characterized by chronic inflammation. In nonobese diabetic mice, resveratrol treatment reduces the expression of inflammatory mediators, like NF-κB, receptors for advanced end glycation products, and NADPH oxidase 4; improves renal pathology; and reduces blood urea nitrogen, serum creatinine, and blood glucose levels as well as hyperglycemia.[79] Furthermore, resveratrol has potent neuroprotective effects by increasing the expression of anti-oxidant enzymes, like superoxide dismutase and glutathione peroxidase, while reducing oxidative reactive oxygen species (ROS), nitric oxide synthase 2 (inducible) (NOS2), and COX-2 via modulating nuclear factor erythroid 2-related factor 2 activation *in vitro* and *in vivo*.[80] Interestingly, resveratrol also has been shown to support immune function in splenic lymphocytes of immunocompromised mice by increasing activation of the c-Jun N-terminal kinase/NF-κB pathway to enhance cytokine expression, peripheral T cell numbers, and splenic lymphocyte proliferation.[81,82] However, how resveratrol treatment causes such opposite effects in different disease models remains to be further explored. Resveratrol has been tested in clinical trials for patients with type 2 diabetes, nonalcoholic fatty liver syndrome, or polycystic ovary syndrome by modulating the expression of transcription factors and cytokines in circulating immune cells.[83,84] Additionally, a recent meta-analysis concluded that resveratrol treatment effectively reduces inflammation and cytokine storms as well as regulates pathways involved in antiviral defense in COVID-19 patients.[85]

Quercetin

Quercetin is a plant pigment of flavonoids that is chemically known as 2-(3,4-dihydroxyphenyl)3,5,7-trihydroxychromen-4-one. It belongs to the family of polyphenols and is a major plant secondary metabolite. Quercetin has many beneficial properties, such as anti-inflammatory, anticancer, anti-oxidant, and antihyperglycemic activ-

ities.[86] Quercetin can inhibit eukaryotic translation by activating a number of kinases, which activate eukaryotic initiation factor 2.[87] It also efficiently scavenges nitrogen and ROS as well as inhibits the activation of NF-κB, mitogen-activated protein kinase (MAPK), and STAT1. Additionally, it stalls the replication of viruses and reduces viral infection.[88–90] On the other hand, quercetin enhances the antiproliferative function of IFN-α by inhibiting hepatocellular carcinoma growth through activating the JAK/STAT pathway, suggesting its differential roles in combating various diseases.[91] In LPS-stimulated human umbilical vein endothelial cells and macrophages, quercetin reduces the levels of COX-2 and NOS2 expression by suppressing activator protein-1, NF-κB, and STAT1 signaling.[92] Quercetin treatment inhibits the expression of ICAM-1 in PMA- or TNF-α-stimulated endothelial cells[93] and ICAM-1 expression in pulmonary epithelial cells, which is dependent on the IL-1-activated MAPK1 pathway.[94] *In vivo,* quercetin has potent anti-inflammatory activity in Wister rats with carrageenan-induced inflammation, in C57BL/6J mice fed with a high-fat diet, and in a murine model of airway allergic inflammation. Evidently, quercetin treatment decreases serum TNF-α, regulated on activation, normal T expressed and secreted, prostaglandin E2 (PGE2), IL-4, IL-5, and IFN-α levels in rodents and reduces NF-κB activation, P-selectin expression, and eosinophil recruitment to bronchoalveolar lavage fluid in airway allergic inflammatory models.[95–97] Interestingly, quercetin is a natural ligand of aryl hydrocarbon receptors, which are expressed on immune cells, partially explaining its immunomodulation.[98] In human dendritic cells, engagement of high expression of aryl hydrocarbon receptors by quercetin reduces T cell activation and migration by downregulating CD83 expression.[99] Moreover, quercetin treatment also downregulates the expression of immunoglobulin-like transcripts 3–5, disabled adaptor protein 2, and ectonucleotidases of CD39 and CD73 as well as IL-12. Thus, quercetin induces immunotolerogenic responses in human dendritic cells.[99] Actually, treatment with a hydrogel containing sodium alginate/bioglass and quercetin inhibits inflammation by inducing M2 macrophages and reducing inducible nitric oxide synthase (iNOS) expression, matrix degradation, and inflammatory infiltrates in a rat model of articular cartilage defects.[100] Another study indicates that quercetin treatment facilitates M2 polarization as well as reduces intracellular ROS and caspase 3-mediated chondrocyte apoptosis, ameliorating osteoarthritis in rats.[101] These anti-inflammatory effects of quercetin are associated with inhibition of the Akt/NF-κB signaling in IL-1β-treated chondrocytes.[101] The anti-oxidant and anti-inflammatory activities of quercetin have also been evaluated in multiple *in-vivo* models of sepsis. The results indicate that treatment with quercetin decreases the levels of COX-2, MDA, and nitrates but increases the expression of the anti-oxidants glutathione, glutathione peroxidase, superoxide dismutase, and catalase, accompanied by downregulation of NF-κB activation and expression of the pro-inflammatory molecules TNF-α, IL-1β, IL-6, and high-mobility group box 1 protein.[102] A combination of quercetin and vitamin C also has been advocated to ameliorate respiratory infections, such as COVID-19, due to their synergistic antioxidant role.[103] Clinical trials have revealed that quercetin has successfully reduced oxidative stress, IL-8, and TNF-α levels in sarcoidosis patients.[104] Additionally, this molecule has shown some beneficial effects in patients with cardiovascular diseases.[105]

Epigallocatechin-3-gallate (EGCG)

This component is an active molecule present in copious amounts in green tea, *Camellia sinensis* (Theaceae), and is chemically known as [(*2R*,*3R*)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-*2H*-chromen-3-yl]3,4,5-trihydroxybenzoate. EGCG has antiproliferative, anti-oxidant, anti-inflammatory, and anti-angiogenic activities.[106–109] EGCG can downregulate NF-κB activation by preventing the degradation of IκB.[110,111] Additionally, it also inhibits the MAPK pathway and the proliferation of tumor cells.[112,113] It works as an anti-apoptotic molecule by downregulating the expression of Bax and caspase 3.[114–117] Its anti-inflammatory role is further demonstrated in proteolipid protein-induced experimental autoimmune encephalomyelitis mice. Treatment with EGCG effectively decreases TNF-α production and proteolipid protein-specific T cell proliferation *ex vivo*.[118] It also inhibits delayed-type hypersensitivity skin responses and reduces serum IFN-γ, IL-17, IL-6, and IL-1β levels in mice by downregulating the expression of transcription factors such as Tbet and RORγt, which are crucial for Th1 and Th17 differentiation, respectively.[119] The modification of T cell responses by EGCG is also observed in mouse models of diet-induced obesity-related inflammation as well as mice with collagen-induced arthritis.[120] Mechanistically, EGCG treatment enhances STAT5 activation but attenuates STAT3 activation to promote regulatory T cell responses, thus mitigating Th17 responses in these obese models.[120] It is possible that EGCG may regulate epigenetic modifications of *FoxP3*, enhancing regulatory T cell responses.[121] The anti-inflammatory capacity of EGCG is able to ameliorate *Porphyromonas gingivalis*-induced atherosclerosis in apolipoprotein E-deficient mice by lowering the levels of serum monocyte chemoattractant protein-1 and acute phase C-reactive protein.[122] Besides, EGCG treatment also decreases the relative levels of iNOS, matrix metalloproteinase-9, lectin-like oxidized low-density lipoprotein, CCL-2, ICAM-1, and NADPH oxidase-4 mRNA transcripts in the aorta of mice but increases heme oxygenase-1 expression.[122] Interestingly, EGCG treatment can increase CD3, CD19, and Mac-3 expression, suggesting an increase in the numbers of T cells, B cells, and macrophages, respectively, and enhances the phagocytic activity of macrophages from peripheral circulation.[123]

Clinically, EGCG has been tested in a number of trials. While there was no significant change in the level of serum C-reactive protein, IL-1, IL-6, or adiponectin, EGCG was well tolerated in 35 obese subjects with metabolic syndrome.[124] Topical administration of EGCG ameliorates inflammatory and noninflammatory acne lesions in an 8-week randomized clinical trial for acne vulgaris. Antimicrobial activity of EGCG against *Propionibacterium acnes* also has been demonstrated.[125] Another study has shown that treatment with EGCG increases the apoptosis of circulating B cells in patients with chronic B cell lymphocytic leukemia by inhibiting vascular endothelial growth factor receptor signaling and downregulating the expression of anti-apoptotic Bcl2, X-linked inhibitor of apoptosis protein, and myeloid cell leukemia-1.[126] The National Institute of Health, USA has initiated 91 interventional clinical trials for EGCG, highlighting the therapeutic potential of this polyphenol (https://www.clinicaltrials.gov/ct2/results?cond=&term=Epigallocatechin-3-gallate&cntry=&state=&city=&dist=%20).

Luteolin

Luteolin or 3′,4′,5,7-tetrahydroxyflavone is a flavonoid molecule with the backbone of 2-phenylchromone and can be extracted from the flowers of the marigold plant[127] and other sources such as chamomile tea, oranges, celery, broccoli, honeysuckle, among others.[128] Luteolin has neuroprotective, antineoplastic, anti-inflammatory, and anti-allergic activities. *In-vitro* studies have shown that luteolin reduces TNF-α and IL-6 release by LPS-treated RAW 264.7 cells, which is attributed to inhibition of the NF-κB- and

MAPK-associated transcription factor ERK, p38, and AP-1 expression.[13,129,130] Luteolin can help to inhibit T cell responses and IFN-γ production in both murine and human autoreactive T cells following challenge with alpha B-crystallin, which is an autoantigen-related to multiple sclerosis.[131] Moreover, luteolin treatment reduces lymphocyte infiltration in the thyroid gland as well as downregulates IFN-γ, TNF-α, and COX-2 expression and the STAT1 and STAT3 signaling pathways during T cell activation in a mouse model of experimental autoimmune thyroiditis.[132] Additionally, luteolin treatment ameliorates clinical symptoms and inhibits autoreactive T cell responses and IFN-γ production in an animal model of experimental autoimmune encephalomyelitis.[133] Luteolin decreases leukocyte infiltrates and 6-keto-prostaglandin F1-alpha and COX-2 expression in mice with carrageenan-induced paw edema.[14] Furthermore, luteolin inhibits the interaction of monocytes and endothelial cells by reducing the levels of ICAM-1 and vascular cell adhesion protein-1 (VCAM-1) expression in an animal model of TNF-α-induced atherosclerosis. It also reduces the levels of monocyte chemoattractant protein-1 expression and $F4/80^+$ macrophage infiltrates in the aorta of mice, demonstrating its anti-inflammatory effect.[134] A randomized double-blind controlled clinical trial has shown that topical application of luteolin reduces skin erythema post ultraviolet B-ray irradiation in 40 subjects.[135] Finally, luteolin is reported to be much safer than quercetin as a dietary supplement.[136]

Colchicine

Colchicine is known as a tropolone derivative, and its chemical structure is *N*-[(*7S*)-1,2, 3,10-tetramethoxy-9-oxo-6,7-dihydro-*5H*-benzo(a)heptalen-7]-ylacetamide. This bioactive molecule is a major component of *Colchicum autumnale*. The mechanism of colchicine has been extensively studied with respect to damaging microtubule dynamics. Functionally, colchicine can inhibit T cell activation by downregulating the expression of IL-2 receptor and lymphocyte function-associated antigen 1 in human lymphocytes.[137] In contrast, colchicine also has been used as an adjuvant to elicit ovalbumin-induced T cell responses, suggesting its dual roles in T cell immunity.[138] Recently, colchicine derivatives have been shown to enhance the survival of allografts by inhibiting T cell differentiation and responses.[139] Colchicine can activate nuclear factor erythroid 2-related factor 2 in hepatocytes to release hepatokines, such as growth differentiation factor 15, which inhibits the activation of myeloid cells, thus impairing their anti-inflammatory function.[140] Colchicine has been approved by the Federal Drug Administration as a drug to treat Mediterranean fever and acute gout flares.[141–143] Colchicine, along with other anti-inflammatory drugs, is used as a combinatorial therapy to reduce the recurrence or incessant pericarditis.[144,145] Importantly, colchicine has been considered a potential drug candidate for the treatment of COVID-19 patients because of its diverse anti-inflammatory properties.[146] A clinical study has further validated that colchicine treatment increases the discharge rate and decreases mortality in COVID-19 patients, accompanied by changes in lymphocyte numbers, lymphocyte-to-neutrophil ratios, and C-reactive protein amounts.[147,148]

Capsaicin

Capsaicin is chemically known as (*E*)-*N*-[(4-hydroxy-3-methoxyphenyl) methyl]-8-methylnon-6-enamide and is a hydrophobic alkaloid present in chili peppers, *Capsicum* species, and the Solanaceae family. Historically, capsaicin has been used as a traditional medicine to combat pain. In fact, capsaicin is an agonist for transient receptor potential channel vanilloid subfamily member 1 (TRPV1),[149,150] a Ca^{2+} channel that can be activated by various stimuli, such as pH, temperature, and others, to induce the sensation.[151] Continuous stimulation by capsaicin, in turn, causes desensitization of these receptors, reducing the pain signals in neurons.[152,153] Immunologically, capsaicin can reduce the levels of iNOS, NF-κB, and COX-2 expression in macrophages in a TRPV1-dependent manner.[154] However, other studies report that capsaicin upregulates COX-2 expression in primary sensory neuronal cells, suggesting that capsaicin may have differential effects on COX-2 expression, based on the cell type.[155] Actually, capsaicin blocks Jurkat cell activation by inhibiting the receptor-mediated Ca^{2+} entry.[156] It also inhibits the proliferation of human T-cell leukemia virus type 1-associated chemoresistant adult T leukemia cells.[157] Furthermore, the oral administration of capsaicin reduces T cell activation and proliferation in pancreatic lymph nodes, ameliorating the symptoms of type 1 diabetes in mice in an IL-10-dependent manner.[158] In addition, capsaicin inhibits natural killer cell functions and TNF-α production. Capsaicin elicits its effects by binding to its receptor TRPV1.[159] Capsaicin is also known to reduce paw inflammation in arthritic rats[154,160] and attenuates the corticosterone-caused immune suppression in mice by reducing IL-10, IL-4, and transforming growth factor-β1 levels.[161] One meta-analysis indicates that capsaicin is indeed efficient against osteoarthritis in a clinical setting.[162] Finally, a cutaneous patch containing 8% capsaicin has been approved by the European Union for nondiabetic individuals to treat nephropathic pain.[6]

Terpenes and their derivatives

Terpenes belong to the largest class of secondary metabolites and are made of a backbone of five carbon isoprenoid units (C5H8).[163] Terpenes can be classified based on the number of repeating isoprenoid units into hemiterpene, monoterpene, sesquiterpene, and diterpene with one, two, three, and four isoprenoid units, respectively. Terpenoids are modified terpenes, which may have different functional groups, rearrangements, or, more commonly, oxidized groups. These molecules have potent anti-inflammatory,[164] antioxidant,[165] and antibacterial activities.[166]

The sesquiterpenoids are a special class of terpenoids, and sesquiterpene lactones are primary examples of plant-based immunomodulators. Sesquiterpene lactones are major bioactive molecules that are derived from the plants belonging to the family *Asteraceae*.[167] Sesquiterpene lactones can inhibit T cell receptor-mediated T cell activation *in vitro*. Similarly, the terpenoids, such as grosheimin, agracin, parthenolide, argablin, and estafiatin, by virtue of their α-methylene-γ-lactone backbone, can inhibit the CD3-mediated Ca^{2+} mobilization and signaling in T cells, which blocks ERK phosphorylation.[168] On the contrary, other studies have reported that sesquiterpene lactones, such as 7-hydroxy frullanolide, inhibit both $CD4^+$ T cell activation and peritoneal macrophage responses by opening up plasma membrane Ca^{2+} channels to increase intracellular Ca^{2+} levels.[169] Parthenolide can reduce NF-κB signaling by preventing its binding to DNA and enhancing IκB-kinase activity.[170] The sesquiterpene lactone fraction extracts from *Artemissia khorassanica in vitro* can inhibit the production of NO and PGE_2 by downregulating COX and iNOS expression in macrophages. Moreover, treatment with sesquiterpene lactones shifts an IFN-γ-based Th1 response to an IL-4-producing Th2 response, highlighting their therapeutic potential.[171] Artemisinin, thapsigargin, and parthenolide are the sesquiterpene lactones that have been approved for clinical

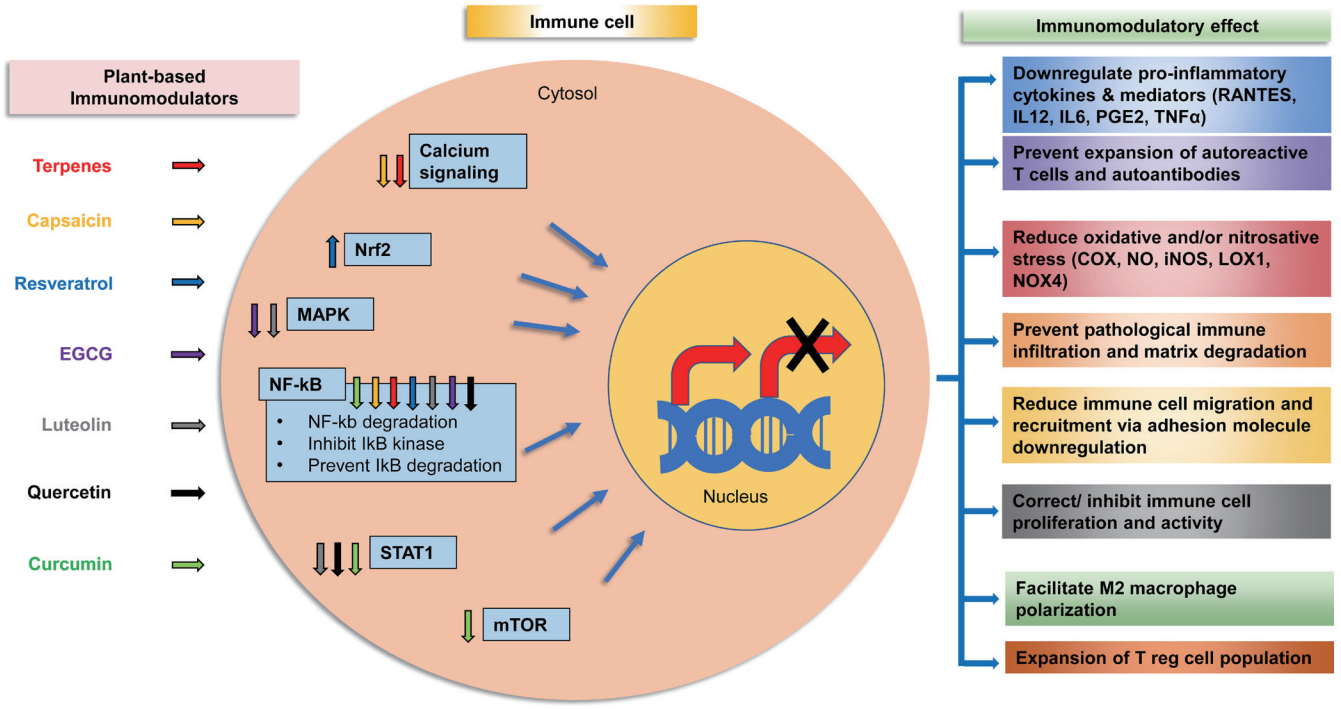

Fig. 3. Schematic representation of plant-based immunomodulators (EGCG: epigallocatechin gallate) and their effects on different cell-signaling pathways. The pathways include the mitogen-activated protein kinase (MAPK), nuclear factor erythroid 2-related factor 2 (Nrf2), nuclear factor kappa-light-chain-enhancer of activated B cells, signal transducer and activator of transcription 1 (STAT1), and mammalian target of rapamycin (mTOR) pathways. The downstream immunomodulatory effects include downregulation of pro-inflammatory mediators and cytokines such as regulated on activation, normal T expressed and secreted (RANTES), interleukin-12 (IL-12), interleukin-6 (IL-6), prostaglandin E2 (PGE2), tissue necrosis factor alpha (TNFα). Additionally, they can also affect the mediators involved in the generation of oxidative and nitrosative stress such as cyclooxygenase (COX), nitric oxide (NO), inducible nitric oxide synthase (iNOS), lectin-like oxidized low-density lipoprotein (LOX1), and NADPH oxidase 4 (NOX4), which are all involved in immune cell responses. These cause an array of changes with respect to the immunomodulatory effects that the compounds modulate.

trials as anticancer and anti-inflammatory drugs.[172]

Future perspectives

There is a plethora of traditional plant-based medicines with documented evidence of their beneficial effects, although the exact cellular and molecular mechanisms underlying their actions are still unknown. We have discussed the therapeutic potentials of some of the important plant-based immunomodulators and their pharmacological actions in regulating various immune responses (Fig. 3). However, the field of plant-based immunomodulation is still in its infancy as many plant-based extracts and compounds remain undiscovered and the mechanisms underlying their actions are still poorly understood. Therefore, further studies in this field are of utmost importance. Given the vastness of the recorded medicinal plants and their effects, plant-based immunomodulators are goldmines for future research and may be the alternative to combat dysregulated immune response-related diseases.

Conclusions

The immune system is an indispensable component for the host's survival as it provides efficient protection via its diverse array of immune cells, protein components, and cell signaling cascades, functioning in complex networks to eradicate a myriad of different pathogens. However, the immune system is less than perfect and, depending on the types of extrinsic or intrinsic factors, immune responses may become dysfunctional to induce autoimmunity, hypersensitivity, and cancer. Autoimmune diseases are increasing the global health burden and are estimated to increase by 3.7% yearly for neurological diseases and 6% for endocrinal, gastrointestinal, and rheumatic diseases.[173] Meanwhile, another major problem is the health burden due to cancer, and the World Health Organization has predicted that new cancer cases will increase at a rate of 15 million yearly by 2020.[174] In 2018, the World Health Organization estimated that the annual emergence of cancer cases was about 18.1 million, which is approximately 3 million cases more than what was previously predicted.[175] Furthermore, the COVID-19 pandemic has become the most recent problem, with most deaths in the Intensive Care Unit due to severe inflammation, which causes multiple organ dysfunction and failure.[176] Immunomodulators modulate the dysfunctional immune responses during the pathogenic process of various diseases. Although there are a number of conventional immunomodulators available in the clinic, they may have varying adverse effects. Accordingly, alternative immunomodulators, such as plant-based immunomodulators, should be considered as a new option given their minimum side effects and cost effectiveness.

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Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

Contributed to the study concept and design (SP and DPN), acquisition of the data (SP and JF), analysis and interpretation of the data (SP and DPN), writing and drafting of the manuscript (SP, JF, and DPN), critical revision of the manuscript (SP, JF, and DPN) and supervision (DPN).

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