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Review article

Role of ginsenosides, the main active components of *Panax ginseng*, in inflammatory responses and diseases

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ABSTRACT

Panax ginseng is one of the most universally used herbal medicines in Asian and Western countries. Most of the biological activities of ginseng are derived from its main constituents, ginsenosides. Interestingly, a number of studies have reported that ginsenosides and their metabolites/derivatives—including ginsenoside (G)-Rb1, compound K, G-Rb2, G-Rd, G-Re, G-Rg1, G-Rg3, G-Rg5, G-Rh1, G-Rh2, and G-Rp1—exert anti-inflammatory activities in inflammatory responses by suppressing the production of proinflammatory cytokines and regulating the activities of inflammatory signaling pathways, such as nuclear factor-κB and activator protein-1. This review discusses recent studies regarding molecular mechanisms by which ginsenosides play critical roles in inflammatory responses and diseases, and provides evidence showing their potential to prevent and treat inflammatory diseases.

1. Introduction

The immune response is the most important defense system protecting the human body from external attacks by microorganisms and toxic chemical compounds. In order for this function to work properly, it is necessary to distinguish pathogens from the body's own cells or tissues. However, pathogens can avoid the immune system through various mechanisms. Therefore, multiple approaches that recognize and neutralize pathogens have been developed to overcome these difficulties. The immune system uses a layered defense strategy against infection based on gradually increasing specificity for invading organisms [1]. Innate immunity is the first line of defense, composed of four kinds of barriers: physical, physiological, phagocytosis, and inflammation (Table 1). Innate immunity acts mainly to detect invading microorganisms by recognizing their pathogen-associated molecular patterns [2], and therefore acts in a comprehensive manner against pathogens. In addition, the immune response is not long-lasting [3]. Adaptive immunity, also known as acquired immunity, is the second line of defense and has two important processes that are distinguished from those of innate immunity: presenting antigens and developing immunological memory (Table 2) [4]. Adaptive immunity is divided into two types of immune responses: humoral immune response and cell-mediated immune response [5]. The humoral immune response is mediated by antibodies produced by B cells in body fluids, which collaborate with complements secreted by hepatocytes or macrophages [4,6]. The cell-mediated immune response refers to the process in which immune cells detect and destroy nonself cells [7], and consists of two responses. Of the two, the antigen-specific reaction is caused by cytotoxic T cells that are produced to destroy antigen-displaying cells by recognizing major histocompatibility complex class I molecule- and endogenous antigen-presenting cells, whereas nonspecific reactions take place when major histocompatibility complex class II molecules and exogenous antigens are presented on the cell membrane. In this response, helper T cells are produced and secrete interleukins and cytokines to stimulate B cells [8]. In turn, the stimulated B cells produce antigen-specific antibodies and activate natural killer cells and macrophages to eliminate the infected cells [9].

Ginseng, a perennial plant belonging to genus *Panax*, family Araliaceae, has been used as a popular herbal medicine for thousands of years. Ginseng is known to promote vitality, prolong life,

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Table 1
The four barriers of innate immunity

Physical barriers	Skin	Skin epidermis prevents pathogen invasion Skin pH maintained between 3 and 5 by sebum to inhibit growth of pathogens
	Mucosal membrane	Mucosal membrane traps pathogens
Physiological barriers	Temperature	Temperature affects survival of invading pathogens
	pH	Acidic environment of stomach kills pathogens
	Chemical mediators	Lyse cell walls of invading pathogens
Phagocytosis	Neutrophils, macrophages, dendritic cells	
Inflammation	Clearing invading pathogens via complex events	

Table 2
Innate versus adaptive immunity

	Innate immunity	Adaptive immunity
Specificity	Broad specificity	Narrow specificity
Memory	Absent	Present (amplified in second response)
Cells	Macrophages, dendritic cells, neutrophil cells	B and T lymphocytes
Reaction time	Immediate response	Delayed response
Receptors	Encoded in the germline (LPS receptor, *N*-formyl methionyl receptor, mannose receptor, and scavenger receptor)	Encoded by somatic genes diversified by somatic recombination (TCR, Ig)

Ig, immunoglobulin; LPS, lipopolysaccharide; TCR, T cell receptor.

and show effects against a variety of conditions, including depression, diabetes, fatigue, aging, inflammation, internal degeneration, nausea, tumors, pulmonary problems, dyspepsia, vomiting, nervousness, stress, and ulcers [10–14]. There are up to 13 plants affiliated with the genus *Panax*, with just five of them used therapeutically: *Panax ginseng*, American ginseng, Vietnamese ginseng, Japanese ginseng, and Pseudoginseng. Among these five, *P. ginseng* is most commonly used for the purpose of treatment, being used in 16.6% of 3,944 prescriptions reported in the *Korean Clinical Pharmacopoeia*, written in 1610 A.D. [15]. The pharmacological effects of ginseng are derived from multiple active ingredients, including ginsenosides, ginsengosides, polysaccharides, peptides, phytosterols, polyacetylenes, polyacetylenic alcohols, and fatty acids [16,17].

The ginsenosides are the major active pharmacological components of ginseng [18]. Ginsenosides, also known as steroid-like saponins, are unique to ginseng species. There are more than 100 ginsenosides, which are expressed by Rx. The X is determined by the distance of movement on a thin-layer chromatography plate *in vitro*: the most polar segment is marked A, whereas the least polar is H [19]. Ginsenosides are classified into four groups based on their backbone types (Fig. 1). Diverse sugar molecules are attached to different areas of the four backbones to produce distinctive ginsenoside molecules (Table 3). Various studies have been conducted to understand the pharmacological mechanisms of ginseng and ginsenosides in cardiovascular disease, diabetes mellitus, cancers, stress, and immunostimulation [18]. The anti-inflammatory role of ginseng, however, remains poorly understood. Therefore, the pharmacological functions of ginseng and ginsenosides in inflammatory responses are discussed in this review.

2. Inflammatory responses and cytokines

Inflammation is a protective response of the body to remove harmful stimuli, including damaged cells, pathogens, and irritants [20], and is one of the physical barriers of innate immunity. Infection by pathogens is a main cause of inflammatory responses, but injury or trauma (in the absence of parasitic infection) and exposure to foreign particles, irritants, and pollutants are also potent inducers of inflammation [21]. Inflammation is a well-orchestrated biological reaction that consists of multiple steps. The first step is the recognition of external stimuli. This is mainly achieved by germ-line encoded receptors, such as Toll-like receptors (TLRs) and leucine-rich-repeat-containing receptors (NLRs) [22–24]. These receptors detect pathogen- or damage-associated molecular patterns, then activate receptors to stimulate a series of signaling cascades, including nuclear factor-kappa B (NF-κB) and activator protein-1 (AP-1) pathways. These transcriptional factors induce the expression of proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and interferon-gamma (IFN-γ). Consequently, cytokines facilitate the recruitment of effector immune cells to the site of inflamed tissue, and in turn, these effector cells create a cytotoxic environment to remove the invading pathogens by releasing toxic chemicals, including highly reactive oxygen species (ROS) and nitrogen species.

Inflammation is essential to restore tissue homeostasis, and therefore may cause serious diseases when it is not tightly regulated. For example, genetic deficiencies in primary regulators of inflammation increase susceptibility to infection in humans, such as neutropenia. A study using knockout mice revealed that defects in proinflammatory cytokines and effector-encoding genes increase the risk of severe infection [25]. In contrast, immoderate inflammation results in devastating impacts by causing unnecessary collateral damage. An example corresponding to this effect is chronic inflammation, in which acute inflammation persists for more than 4 weeks. Chronic inflammation is caused by persistent injury or infection, prolonged exposure to a toxic agent, or autoimmune disease, which can induce various diseases, such as cancer and diabetes (Fig. 2) [26–29].

3. Anti-inflammatory effects of ginsenosides

3.1. Ginsenoside-Rb1

Ginsenoside-Rb1 (G-Rb1), a main component of *P. ginseng*, inhibits TNF-α production in lipopolysaccharide (LPS)-stimulated RAW264.7 macrophages, indicating that G-Rb1 is a potential anti-inflammatory agent [30,31]. G-Rb1 also suppresses the activation

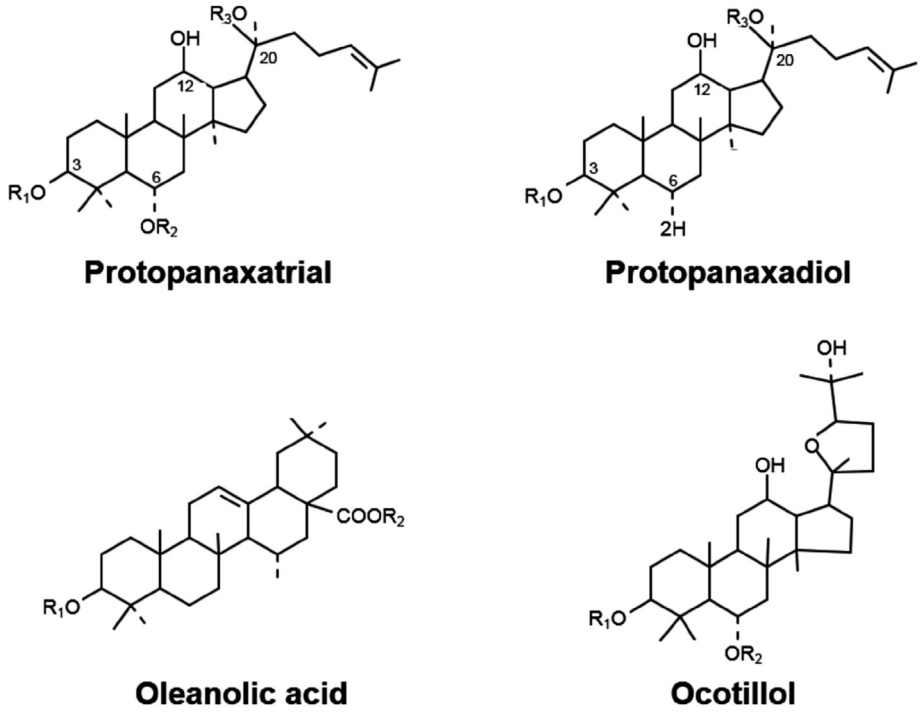

Fig. 1. Classification of ginsenosides based on backbone types.

Table 3
Classification of ginsenosides

Class	Backbone type	Representative ginsenosides
Protopanaxadiol type	Dammarane backbone	Ginsenoside-Ra1-3, G-Rb1-2, and G-Rh2-3
Protopanaxatriol type	Additional hydroxyl group on C6 in a dammarane backbone	Ginsenoside-Re, G-Rf, and G-Rg1
Oleanolic acid type	Pentacyclic triterpenoid base	Ginsenoside-Ro
Ocotillol type	Five-membered epoxy ring at C20	Makonoside-Rs from Vietnamese ginseng

of NF-κB, which is a key regulator of inflammation, as well as a controller of TNF-α production in LPS-activated murine peritoneal macrophages [32]. The activation of IL-1 receptor-associated kinase (IRAK)-1, an inhibitor of κB (IκB) kinase (IKK)-α, NF-κB, and mitogen-activated protein kinases (MAPKs), is also significantly decreased by G-Rb1. However, G-Rb1 does not affect the interaction between LPS and TLR4 and the activation of IRAK-4 and IRAK-2 [32]. In addition, G-Rg1 exhibits *in vivo* anti-inflammatory effects in a 2,4,6-trinitrobenzene sulfuric acid (TNBS)-induced colitis animal model by inhibiting IRAK activation-mediated inflammatory responses [32].

Osteoporosis is a bone loss disease characterized by decreased bone strength and increased bone fragility [33]. Osteoporosis occurs as a result of a variety of endocrine, metabolic, and mechanical factors [34]. However, the influence of inflammation on bone turnover has also emerged. In particular, inflammatory diseases such as immunological dysfunctions, autoimmune and chronic inflammatory diseases, HIV infection, hyper-immunoglobulin E (IgE) syndrome, rheumatoid arthritis, hematological diseases (particularly myeloma), and inflammatory bowel diseases are related to osteoporosis [35–39]. Inflammation mainly regulates bone remodeling through two mechanisms [40]. (1) Proinflammatory cytokines play roles as final regulators of osteoclast function. For example, the receptor activator of NF-κB ligand (RANKL), also known as TNF-related activation-induced cytokine, belongs in this category. (2) Regulation of macrophage colony stimulating factor controls osteoclastogenesis [41]. Interestingly, G-Rb1 exerts antiosteoporotic activity by inhibiting the RANKL-stimulated osteoclast differentiation from RAW264.7 macrophages. G-Rb1 suppresses RANKL-induced c-Jun N-terminal kinases (JNKs), p38 MAPK, and NF-κB pathways, and consequently blocks the expression of c-Fos and NF of activated T cells (NFAT) C1, which are essential factors for the differentiation of osteoclasts [42].

3.2. Compound K

Compound K (CK), a bacterial metabolite of G-Rb1, exhibits anti-inflammatory effects mainly by reducing inducible nitric oxide synthase (iNOS), cyclooxygenase (COX)-2, and proinflammatory cytokines [32,43,44]. CK suppresses the expression of proinflammatory cytokines by downregulating the activities of IRAK-1, MAPKs, IKK-α, and NF-κB in LPS-treated murine peritoneal macrophages [32]. CK also suppresses the expression of iNOS and COX-2 by inhibiting NF-κB signaling in LPS-stimulated RAW264.7 cells [45]. In zymosan-treated bone-marrow-derived macrophages (BMDMs) and RAW264.7 cells, CK inhibits inflammatory responses by negatively regulating the secretion of proinflammatory cytokines, the activation of MAPKs, and the generation of ROS [43]. In addition, anti-inflammatory activity of CK has been observed in LPS-stimulated microglial cells. CK hinders inflammatory responses by controlling both the generation of ROS and the activities of MAPKs, NF-κB, and AP-1 [44].

The anti-inflammatory activities of CK have been explored in a variety of inflammation-associated animal models. CK

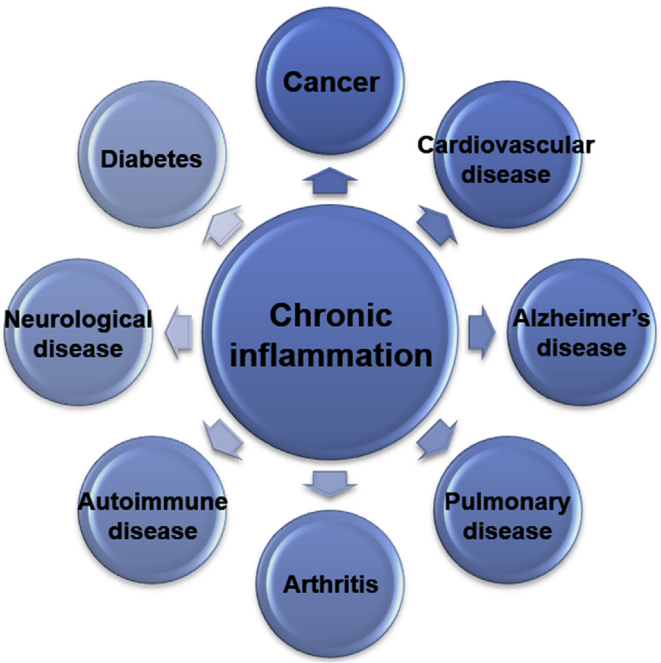

Fig. 2. Diseases associated with chronic inflammation.

downregulates 12-*O*-tetradecanoylphorbol-13-acetate-induced ear edema by regulating the activities of NF-κB and COX-2 [46]. CK negatively regulates intestinal inflammation by modulating NF-κB signaling in both a TNBS-induced colitis animal model and a dextran sulfate sodium-induced colitis animal model [32,47]. Moreover, CK protects mice from endotoxin-induced lethal shock by inhibiting the production of proinflammatory cytokines [43,48].

3.3. Ginsenoside-Rb2

Ginsenoside-Rb2 (G-Rb2) significantly inhibits the production of TNF-α in LPS-stimulated RAW264.7 cells and differentiated U937 cells with IC_{50} values of 27.5 μM and 26.8 μM, respectively [31]. In addition, G-Rb2 has been reported to exert neuroprotective effects in LPS-stimulated N9 microglial cells by blocking TNF-α production [49]. G-Rb2 inhibits activation of IκBα, indicating that G-Rb2-mediated downregulation of TNF-α production in microglia is achieved by NF-κB inhibition, which may be a basic mechanism for the anti-inflammatory activity of G-Rb2 [49].

3.4. Ginsenoside-Rd

Ginsenoside-Rd (G-Rd) has also shown neuroprotective effects. Similar to G-Rb2, G-Rd also suppresses LPS-stimulated NF-κB activation and TNF-α expression in N9 cells [49]. In addition, G-Rd exerts neuroprotective effects in a rat model of transient focal cerebral ischemia by regulating an early free radical scavenging pathway and a late anti-inflammatory response. G-Rd also decreases the formation of hydroxyl radicals, the early accumulation of DNA and protein, and lipid peroxidation. G-Rd suppresses inflammatory responses in later stages after ischemia by the inhibiting the expression of iNOS and COX-2 [50]. Moreover, G-Rd deceases inflammatory responses in LPS-treated RAW264.7 cells. G-Rd reduces NO generation, PGE_2 production, and NF-κB activity [51].

3.5. Ginsenoside-Re

Ginsenoside-Re (G-Re) shows anti-inflammatory effects by inhibiting interactions between LPS and TLR4 on macrophages. G-Re suppresses LPS-mediated phosphorylation and degradation of IRAK-1, and sequentially blocks IKK-α phosphorylation, NF-κB activation, and the expression of proinflammatory cytokines, such as TNF-α and IL-1β [52].

LPS-induced inflammatory response is closely associated with neurodegenerative diseases, including Parkinson disease, Alzheimer disease (AD), and multiple sclerosis. It has been known that LPS activates microglial cells in the central nervous system [53,54]. G-Re exerts a protective effect against neuroinflammation in the central nervous system by inhibiting proinflammatory mediators (iNOS and COX2) generated by LPS and blocking the p38 MAPK signaling pathway in BV2 microglial cells, indicating that G-Re could be a promising medication to treat neuroinflammatory diseases [55]. G-Re is curative in a TNBS-induced colitis mouse model. Oral administration (20 mg/kg) of G-Re is effective against LPS-induced systemic inflammation in a TNBS-induced colitis mouse model. G-Re dramatically inhibits the expression of IL-1β and TNF-α, as well as NF-κB activation, and suppresses colon shortening and myeloperoxidase activity in a colitis mouse model [52].

3.6. Ginsenoside-Rg1

Ginsenoside-Rg1 (G-Rg1) modulates microglial activation, which plays a critical role in neurodegenerative diseases. G-Rd1 negatively regulates the production of TNF-α and NO as well as the expression of iNOS and ionized calcium-binding adapter molecule 1 (Iba-1) by inhibiting the activation of NF-κB and MAPKs pathways in mice when LPS is intracerebroventricularly injected [56]. In accordance, G-Rg1 also suppresses the expression of iNOS, COX-2, TNF-α, IL-1β, and NF-κB in LPS-stimulated BV-2 microglial cells. Interestingly, PLC-γ1 inhibitor partially eliminates the suppressive effect of G-Rg1 in the LPS-mediated activation of IκB-α, cAMP response element-binding protein (CREB), extracellular signal-regulated kinase 1/2 (ERK1/2), JNK, and p38 MAPK, indicating that PLC signaling may be associated with the inhibitory activity of G-Rb1 for microglial activation [57,58]. The inhibitory activity of G-Rg1 on inflammation has also been examined in macrophages. G-Rg1 suppresses the expression of both IL-6 mRNA and protein by inhibiting the NF-κB signal pathway in both LPS-stimulated RAW264.7 cells and mouse peritoneal macrophages. In contrast, G-Rb1 increases TNF-α expression by activating the mTOR signaling pathway in LPS-stimulated macrophages [59]. These results strongly suggest that G-Rg1 plays a pivotal role in macrophage-mediated inflammatory responses with different modes of actions by modulating signaling pathways of NF-κB or Akt/mTOR. *In vivo* anti-inflammatory function of G-Rg1 has also been demonstrated in inflammatory animal models. G-Rg1 effectively ameliorates the symptoms of alcoholic hepatitis and TNBS-induced colitis in animal models by inhibiting the activation of the NF-κB signaling pathway, as consistently observed *in vitro* [60,61].

Recently, it was reported that G-Rb1 protects diverse tissues from ischemia/reperfusion (IR) injury by regulating inflammatory response and apoptosis. G-Rb1 protects the liver against IR injury in rats by modulating NF-κB and ROS–NO–hypoxia-inducible factor signaling pathways [62,63]. Cerebral IR injury is also ameliorated by G-Rb1 activating peroxisome proliferator-activated receptor-γ/heme oxygenase-1 (HO-1) or suppressing protease-activated receptor-1 expression in rat hippocampus [64,65]. Moreover, G-Rg1 shows a protective effect against cerebral IR injury by modulating the activation of p38 MAPK [66]. These results suggest that G-Rg1 has therapeutic potential for IR injury.

3.7. Ginsenoside-Rg3

Ginsenoside-Rg3 (G-Rg3) shows suppressive effects in neurodegenerative conditions by preventing inflammatory neurotoxicity and microglial activation. G-Rg3 significantly suppresses TNF-α expression and NF-κB activation in Abeta42-activated BV-2 microglial cells. The survival rate of TNF-α-treated Neuro-2a cells increased after pretreatment with G-Rg3 [67]. In addition, daily administration of G-Rg3 for 21 days significantly improves learning and memory impairments induced by LPS injection into rat brains by inhibiting the expression of inflammatory mediators in the hippocampus [68].

Recent studies have reported the role of G-Rg3 in inflammasome activation. Two optical isomers of G-Rg3, 20(*R*)-Rg3 and 20(*S*)-Rg3, exhibit inhibitory effects on both *S*-nitrosylation of the nucleotide-binding domain leucine-rich repeat-containing receptor pyrin domain-containing 3 (NLRP3) inflammasome and lethal endotoxin-induced shock by suppressing iNOS [69], whereas 20(*R*)-Rg3 and 20(*S*)-Rg3 suppress NO generation and iNOS expression. *S*-nitrosylation of the NLRP3 inflammasome proteins, such as NLRP3 and caspase-1, is decreased by these G-Rg3 isomers in LPS-stimulated peritoneal macrophages and BMDMs. Under long-term LPS exposure, LPS-generates excessive NO that inhibits IL-1β production by inducing inflammasome activation and Akt phosphorylation. However, 20(*R*)-Rg3 and 20(*S*)-Rg3 prevent this event by blocking the excessive generation of NO. Moreover, 20(*R*)-Rg3 and 20(*S*)-Rg3 reduce susceptibility to lethal endotoxin shock by modulating the generation of NO in LPS-injected mice, strongly indicating that these two optical isomers of G-Rg3 might be useful in therapeutic approaches to treat oxidative stress-related diseases [69].

3.8. Ginsenoside-Rg5

Anti-inflammatory effects of ginsenoside-Rg5 (G-Rg5), a main component of steamed ginseng, have been studied in the context of lung inflammation. G-Rg5 reduces the expression of IL-1β, TNF-α, COX-2, and iNOS, and phosphorylation of IRAK-1, IKK-α, and NF-κB. The degradation of IRAK-1 and IRAK4 are decreased by G-Rg5 in LPS-stimulated alveolar macrophages [70]. According to an experiment using Alexa Flour 594-conjugated LPS, G-Rg5 interferes with the binding of LPS to macrophages. The expression of TNF-α, IL-1β, iNOS, and COX-2, as well as the activation of NF-κB are also suppressed by G-Rg5 (10 mg/kg) in the bronchoalveolar lavage fluid of LPS-injected mice [70]. Moreover, the anti-inflammatory activity of G-Rg5 has been observed in TNF-α-stimulated liver cells, and in HepG2 cells by inhibiting NF-κB, COX-2, and iNOS ($IC_{50} = 0.61$) [71].

Inhibitory effects of G-Rg5 in neuroinflammatory responses have also been examined in a memory-impaired rat model induced by streptozotocin (STZ). In particular, because cholinergic system synthases such as choline acetyltransferase, hydrolytic enzymes such as acetylcholinesterase, and imbalanced levels of insulin-like growth factor 1 (IGF-1) and brain derived neurotrophic factor (BDNF) are associated with impaired memory function, the regulatory effect of G-Rg5 on these molecules was investigated. G-Rg5 improves cognitive deficits by downregulating AChE activity and upregulating choline acetyltransferase activity in the cerebral cortex and hippocampus of STZ-induced AD rats. Administration of 10 and 20 mg/kg of G-Rg5 significantly increased the expression of BDNF and IGF-1 in the brain tissue of AD rats. Moreover, amyloid beta (Aβ) deposition was decreased in the hippocampus and cerebral cortex of diseased rats. G-Rg5 suppresses STZ-induced expression of COX-2 and iNOS, which are key inflammatory enzymes in neuroinflammation [72]. In addition, a protective effect of G-Rg5 has been observed in scopolamine-induced memory impaired mice. In this model, G-Rg5 improves memory deficits by suppressing AChE activity and increasing BDNF expression and CREB phosphorylation [73]. Taken together, these findings strongly suggest that G-Rg5 is a potential drug candidate to treat AD.

Anti-inflammatory activity of G-Rg5 in skin tissue was also investigated in *in vitro* atopic dermatitis models, such as TNF-α/IFN-γ-treated keratinocytes and LPS-stimulated macrophages. G-Rg5 dramatically inhibits the expression of thymus- and activation-regulated chemokine (TARC/CCL17) in TNF-α/IFN-γ-stimulated HaCaT cells. LPS-induced generation of NO and ROS is also decreased by G-Rg5 in RAW264.7 cells. In addition, G-Rg5 suppresses NF-κB/p38 MAPK/STAT1 signaling pathways, which are critically involved in TARC/CCL17 expression and NO production [74]. These results indicate that G-Rg5 exerts anti-inflammatory activity in skin disease by blocking the NF-κB/p38 MAPK/STAT1 signal pathways.

3.9. Ginsenoside-Rh1

The anti-inflammatory effects of ginsenoside-Rh1 (G-Rh1) act mainly by suppressing the expression of COX-2 and iNOS [75,76]. In particular, the molecular mechanism of G-Rh1-mediated iNOS inhibition is well demonstrated in microglial cells. In IFN-γ-stimulated BV2 microglial cells, G-Rh1 inhibits the activation of Janus kinase (JAK)/STAT and ERK signaling and their downstream transcriptional factors, including NF-κB, IRF-1, and STAT1, thereby suppressing iNOS expression and neuroinflammation [76].

The inhibitory activity of G-Rh1 on oxazolone-induced atopic dermatitis-like skin lesions in hairless mice has also been investigated. G-Rh1 diminishes the serum levels of IgE and IL-6 in atopic dermatitis-induced mice, and consequently, the infiltration of inflammatory cells and granulation of mast cells significantly decrease. Furthermore, G-Rh1 (10 mg/kg, 20 mg/kg) improves the symptoms of atopic dermatitis and ear swelling [77], suggesting that G-Rh1 has potential as an anti-inflammatory agent for the treatment of atopic dermatitis.

3.10. Ginsenoside-Rh2

Ginsenoside-Rh2 (G-Rh2), an intestinal bacterial metabolite of ginsenoside, has been reported to show anti-inflammatory activity in microglial cells and astroglial cells. In murine BV-2 microglial cells, G-Rh2 inhibits LPS/IFN-γ-induced generation of NO as well as the expression of iNOS, COX-2, TNF-α, and IL-1β, by regulating protein kinase A (PKA)/AP-1 signal pathways [78]. Moreover, G-Rh2 also suppresses TNF-α-induced intercellular adhesion molecule 1 (ICAM-1) expression by suppressing the activities of both NF-κB and JNK/AP-1 signaling pathways in human astroglial cells [79]. Interestingly, G-Rh2-mediated modulation of NF-κB signaling was not observed in either murine microglial cells or human monocytic cells, suggesting that G-Rh2 may inhibit the NF-κB signaling pathway in a cell-specific manner [78,79].

The anti-inflammatory effects of G-Rh2 in allergic airway inflammation have also been investigated in a murine asthma model. G-Rh2 inhibits peribronchiolar inflammation, the recruitment of airway inflammatory cells, cytokine production, total and ovalbumin-specific IgE levels, and expression of aryl hydrocarbon receptor, which are representative pathophysiological characteristics of asthma. Activation of NF-κB and phosphorylation of p38 MAPK are also suppressed by G-Rh2 in this disease animal model [80], indicating that G-Rh2 ameliorates allergic airway inflammation by inhibiting the activation of NF-κB and p38 MAPK. Taken together, G-Rh2 may be useful for the treatment of inflammatory airway diseases, such as asthma.

Table 4
Summary of anti-inflammatory activities of ginsenosides

Ginsenosides	Activities	Models	Mode of action	Ref.
G-Rb1	Anti-inflammation	LPS-treated RAW264.7 cells	Inhibiting TNF-α production	[30,31]
		LPS-treated murine peritoneal macrophages	Blocking activation of IRAL-1, IKK-β, NF-κB, and MAPKs	[32]
		TNBS-induced colitis mice	Inhibiting IRAK-activated inflammatory response	[32]
	Anti-osteoporosis	RANKL-treated osteoblasts differentiated from RAW264.7 cells	Blocking expression of c-Fos and NFATc1 by regulating RANKL-induced JNK, p38 MAPK, and NF-κB	[42]
Compound K	Anti-inflammation	LPS-treated murine peritoneal macrophages	Blocking expression of proinflammatory cytokines by downregulating activities of IRAK-1, MAPKs, IKK-β, and NF-κB	[32]
		LPS-treated RAW264.7 cells	Inhibiting expression of iNOS and COX-2 by suppressing NF-κB	[45]
		Zymosan-treated RAW264.7 cells and BMDMs	Reducing proinflammatory cytokines, MAPKs, and ROS	[43]
		TPA-induced ear edema mice	Inhibiting NF-κB and COX-2	[46]
		TNBS-induced colitis mice	Inhibiting NF-κB	[32]
		DSS-induced colitis mice	Inhibiting NF-κB	[47]
		Endotoxin-induced lethal shock mice	Decreasing expression of proinflammatory cytokines	[43,48]
	Anti-inflammation and neuroprotective effect	LPS-treated microglial cells	Suppressing ROS generation, MAPKs, NF-κB, and AP-1	[44]
G-Rb2	Anti-inflammation	LPS-treated RAW264.7 and U937 cells	Inhibiting TNF-α production	[31]
	Neuroprotective effect	LPS-treated N9 microglial cells	Suppressing TNF-α production via NF-κB inhibition	[49]
G-Rd	Anti-inflammation	LPS-treated RAW264.7 cells	Reducing production of NO and PGE_2, and NF-κB activity.	[51]
	Neuroprotective effect	LPS-treated N9 cells	Suppressing TNF-α and NF-κB	[49]
		Transient focal cerebral ischemia rats	Inhibiting expression of iNOS and COX-2	[50]
G-Re	Anti-inflammation	LPS-treated peritoneal macrophages	Blocking IKK-β phosphorylation, NF-κB activation, and production of proinflammatory cytokines	[52]
		TNBS-induced colitis mice	Inhibiting NF-κB, IL-1β, and TNF-α	[52]
	Anti-neuroinflammation	LPS-treated BV2-microglial cells	Suppressing iNOS, COX-2, and p38 MAPK	[55]
G-Rg1	Neuroprotective effect	LPS-treated BV-2 microglial cells	Suppressing iNOS, COX-2, TNF-α, IL-1β, and NF-κB via PLC-γ1	[57]
		LPS-injected rats	Inhibiting production of TNF-α, IL-1β, and NO via glucocorticoid receptor signaling	[58]
		LPS-injected mice	Inhibiting expression of TNF-α, iNOS, and Iba-1 by blocking NF-κB and MAPKs	[56]
	Anti-inflammation	LPS-treated RAW264.7 cells	(1) Suppressing IL-6 expression by inhibiting NF-κB (2) Increasing TNF-α expression by activation of Akt/mTOR	[59]
		Alcohol-induced hepatitis mice	Inhibiting NF-κB	[60]
		TNBS-induced colitis mice	Inhibiting NF-κB	[61]
	Anti-ischemia reperfusion (IR) injury	Liver IR injury mice	Inhibiting NF-κB and ROS/NO/HIF	[62,63]
		Cerebral IR injury rats	Activating PPAR-γ/HO-1	[64]
		Cerebral IR injury rats	Suppressing PAR-1 expression	[65]
		Cerebral IR injury rats	Modulating p38 MAPK	[66]
G-Rg3	Neuroprotective effect	Abeta42-treated BV-2 microglial cells	Inhibiting TNF-α expression and NF-κB activation	[67]
		LPS-injected rats	Improving learning and memory impairment by inhibiting expression of proinflammatory mediators	[68]
	Anti-inflammation	LPS-treated peritoneal macrophages and BMDMs	Suppressing *S*-nitrosylation of NLRP3 inflammasome by reducing NO generation and iNOS expression	[69]
		LPS-injected mice	Reducing susceptibility to lethal endotoxin shock by regulating NO generation	[69]
G-Rg5	Anti-lung inflammation	LPS-treated alveolar macrophages	Decreasing expression of IL-1β, TNF-α, COX-2, and iNOS by inhibiting NF-κB pathway	[70]
		TNF-α-treated HepG2 cells	Inhibiting NF-κB, COX-2, and iNOS	[71]
		LPS-injected mice	Inhibiting TNF-α, IL-1β, iNOS, COX-2, and NF-κB	[70]
	Anti-neuro inflammation	STZ-induced memory impaired rats	(1) Improving cognitive deficits by downregulating AChE activity and up-regulating ChAT activity (2) Increasing expression of BDNF and IGF-1 (3) Decreasing Aβ deposition (4) Suppressing COX-2 and iNOS	[72]
		Scopolamine-induced memory impaired mice	Improving memory deficits by suppressing AChE activity and increasing BDNF expression and CREB phosphorylation	[73]

	Anti-skin inflammation	TNF-α/IFN-γ-treated keratinocytes	Inhibiting expression of TARC/CCL17 via NF-κB/p38 MAPK/STAT signaling pathways	[74]
		LPS-treated RAW264.7 cells	Reducing generation of NO and ROS	[74]
G-Rh1	Anti-neuro-inflammation	IFN-γ-treated BV2 microglial cells	Inhibiting iNOS expression by suppressing JAK/STAT, ERK, and NF-κB	[76]
	Anti-skin inflammation	Oxazolone-induced atopic dermatitis-like mice	Suppressing production of IgE and IL-6, infiltration of inflammatory cells and granulation of mast cells	[77]
G-Rh2	Anti-neuroinflammation	LPS-/IFN-γ-treated BV-2 microglial cells	Reducing expression of iNOS, COX-2, TNF-α, and IL-1β by suppressing PKA/AP-1	[78]
		TNF-α-treated human astroglial cells	Inhibiting ICAM-1 expression by suppressing NF-κB and JNK/AP-1	[79]
	Anti-airway inflammation	OVA-induced asthma mice	Inhibiting peribronchiolar inflammation by suppressing NF-κB and p38 MAPK	[80]
G-Rh2-B1/G-Rh2-B2	Anti-inflammation	LPS-treated RAW264.7 cells	Reducing expression of TNF-α, IL-6, and IL-1β, and activities of p38 MAPK, JNK, and NF-κB	[81,82]
G-Rp1	Anti-inflammation	LPS-treated RAW264.7 cells	Reducing expression of IL-1β, COX-2, and iNOS by suppressing NF-symbolic kappaB	[83,84]

Aβ, amyloid beta; AChE, acetylcholinesterase; AP-1, activator protein-1; BDNF, brain derived neurotrophic factor; ChAT, choline acetyltransferase; COX-2, cyclooxygenase-2; DSS, dextran sulfate sodium; G-RB1, ginsenoside-Rb1; G-RB2, ginsenoside-Rb2; G-Rd, ginsenoside-Rd; G-Re, ginsenoside-Re; G-Rg1, ginsenoside-Rg1; G-Rg3, ginsenoside-Rg3; G-Rg5, ginsenoside-Rg5; G-Rh1, ginsenoside-Rh1; G-Rh2, ginsenoside-Rh2; G-Rp1, ginsenoside-Rp1; HIF, hypoxia-inducible factor; HO-1, heme oxygenase-1; ICAM-1, intercellular adhesion molecule 1; IFN, interferon; IKK, inhibitor of κB kinase; IL-6, interleukin-6; IL-1β, interleukin-1β; iNOS, inducible nitric oxide synthase; JNK, c-Jun N-terminal kinases; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-kappa B; NO, nitric oxide; OVA, ovalbumin; PKA, protein kinase A; TNBS, 2,4,6-trinitrobenzene sulfuric acid; TNF-α, tumor necrosis factor-alpha; TPA, 12-O-tetradecanoylphorbol-13-acetate.

Unlike other ginsenosides, G-Rh2 exhibits low levels of oral bioavailability and water solubility, and therefore sulfated derivatives of G-Rh2 such as G-Rh2-B1 and G-Rh2-B2 have been synthesized. These derivatives of G-Rh2 reduce LPS-induced production of TNF-α, IL-6, and IL-1β as well as the activities of p38 MAPK, JNK, and NF-κB, showing greater anti-inflammatory effects than that of G-Rh2 [81,82], in turn suggesting that improving bioavailability and water solubility of ginsenosides could also improve their anti-inflammatory effects.

3.11. Ginsenoside-Rp1

Ginsenoside-Rp1 (G-Rp1) has been reported to show anti-inflammatory effects mainly through modulating the activity of NF-κB. G-Rh1 decreases the LPS-induced expression of IL-1β, COX-2, and iNOS by suppressing NF-κB activity in RAW264.7 cells [83,84]. Interestingly, G-Rp1-mediated inhibition of NF-κB activation has been achieved by suppression of IKK-α phosphorylation, but not MAPK phosphorylation [83,84]. These results indicate that G-Rh1 inhibits inflammatory responses specifically by inhibiting NF-κB activation.

4. Conclusion

Studies of the pharmacological roles of ginsenosides have focused mostly on their anticancer, antioxidative, and immunostimulatory activities. A number of recent studies, however, have presented evidence showing that ginsenosides could be used to prevent and treat a variety of inflammatory diseases via anti-inflammatory functions (Table 4). In particular, considering the action mechanisms of ginsenosides, they are expected to regulate inflammatory responses primarily through the inhibition of the NF-κB signaling pathway. In LPS-stimulated macrophages and microglial cells, ginsenosides suppress the production of proinflammatory cytokinases such as TNF-α, IL-1β, and IL-6, as well as inflammatory enzymes, such as iNOS and COX-2. The expression of these molecules is predominantly regulated by NF-κB signaling pathways, where IRAK, IKKα/β, and IκBα are included in inflammatory responses. According to the results of many *in vitro* studies, ginsenosides exert anti-inflammatory activities in a variety of *in vivo* animal models of inflammatory diseases, and show promising protective effects in animal models of colitis, alcohol-induced hepatitis, IR injury, and impaired memory diseases. Furthermore, the biological activities of ginsenoside metabolites, such as CK, G-Rh1, and G-Rh2, have been observed in diverse inflammation models. CK is effective for ameliorating symptoms in animal models of ear edema, colitis, and lethal shock. G-Rh1 and G-Rh1 also exerted anti-inflammatory effects in animal models of atopic dermatitis and asthma.

In conclusion, studies of ginsenosides strongly indicate that ginsenosides and their metabolites/derivatives could serve as potent pharmaceutical agents to prevent and treat inflammatory diseases.

Conflicts of interest

The authors report no conflicts of interest.

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