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Short Review

Roles of ginsenosides in inflammasome activation

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ABSTRACT

Inflammation is an innate immune response that protects the body from pathogens, toxins, and other dangers and is initiated by recognizing pathogen-associated molecular patterns or danger-associated molecular patterns by pattern-recognition receptors expressing on or in immune cells. Intracellular pattern-recognition receptors, including nucleotide-binding oligomerization domain-like receptors (NLRs), absent in melanoma 2, and cysteine aspartate—specific protease (caspase)-4/5/11 recognize various pathogen-associated molecular patterns and danger-associated molecular patterns and assemble protein complexes called "inflammasomes." These complexes induce inflammatory responses by activating a downstream effector, caspase-1, leading to gasdermin D —mediated pyroptosis and the secretion of proinflammatory cytokines, such as interleukin (IL)-1β and IL-18. Ginsenosides are natural steroid glycosides and triterpene saponins found exclusively in the plant genus *Panax*. Various ginsenosides have been identified, and their abilities to regulate inflammatory responses have been evaluated. These studies have suggested a link between ginsenosides and inflammasome activation in inflammatory responses. Some types of ginsenosides, including Rh1, Rg3, Rb1, compound K, chikusetsu saponin IVa, Rg5, and Rg1, have been clearly demonstrated to inhibit inflammatory responses by suppressing the activation of various inflammasomes, including the NLRP3, NLRP1, and absent in melanoma 2 inflammasomes. Ginsenosides have also been shown to inhibit caspase-1 and to decrease the expression of IL-1β and IL-18. Given this body of evidence, the functional relationship between ginsenosides and inflammasome activation provides new insight into the understanding of the molecular mechanisms of ginsenoside-mediated antiinflammatory actions. This relationship also has applications regarding the development of antiinflammatory remedies by ginsenoside-mediated targeting of inflammasomes, which could be used to prevent and treat inflammatory diseases.

1. Introduction

Inflammation is an immune response mainly mediated by innate immune cells, such as macrophages. This response protects the body from invading pathogens and environmental dangers and is characterized by redness, swelling, pain, heat, and loss of function [1—4]. Inflammatory responses are initiated by the interaction of pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) with pattern-recognition receptors (PRRs) expressed on innate immune cells. These recognition molecules include toll-like receptors, C-type lectin receptors, and scavenger receptors. They also include PRRs expressed within immune cells, such as nucleotide-binding oligomerization domain—like receptors (NLRs), leucine-rich repeats (LRRs), absent in melanoma 2 (AIM2), retinoic acid—inducible gene I—like

receptors, and cysteine aspartate—specific protease (caspase)-4/5/11 [5—14]. After PAMPs and DAMPs bind to extracellular PRRs (especially toll-like receptors), intracellular signaling molecules in inflammatory signaling pathways such as the nuclear factor-kappa B, activator protein-1, and interferon-regulatory factor pathways are activated. This activation cascade leads to the expression of inflammatory genes and proinflammatory cytokines, as well as the production of various inflammatory mediators [12,15—17]. Inflammatory responses are also induced by the activation of intracellular PRRs; these intracellular PRR-mediated inflammatory responses differ from those mediated by intracellular PRRs. On distinct stimulation, intracellular PRRs such as NLRs, AIM2, and caspase-4/5/11 assemble protein complexes called "inflammasomes" [10,18]. During the inflammatory responses, inflammasomes are activated and subsequently activate inflammatory caspase-1, resulting in

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gasdermin D (GSDMD)—mediated pyroptosis. This type of pyroptosis is an inflammatory form of programmed cell death. Caspase-1 activation also results in the secretion of proinflammatory cytokines, including interleukin (IL)-1β and IL-18 [8–11,18,19].

Ginseng is a perennial plant in the genus *Panax* that is found in East Asia and North America. Ginseng has been traditionally used as an herbal medicine to alleviate diseases and their symptoms such as diabetes, hypertension, gastric ulcer, neuronal disease, pain, inflammation, and cancer [20–25]. Ginsenosides, which are steroidal triterpenoid saponins, are the main active compounds found in ginseng. These compounds are considered critical constituents for the activities of ginseng against various disease symptoms, including diabetes, cardiovascular disease, stress, cancer, immunostimulation, and inflammation [26–31]. Although many studies have reported that different types of ginsenosides have antiinflammatory activity, the suppressive roles of ginsenosides in inflammatory responses and the underlying molecular mechanisms thereof are not fully understood. Moreover, recent studies have started to focus on the regulatory roles of ginsenosides with respect to the activation of inflammasomes during inflammatory responses.

The present review provides a general introduction to inflammasomes, including their types, structures, and activation. It also discusses recent progress on the regulatory roles of ginsenosides with respect to inflammasome activation in inflammatory responses. The aim of this review is to promote better understanding of the functional relationship between ginsenosides and inflammasome activation and also to provide insight into the development of inflammasome-targeting drugs containing ginsenosides, with the goal that such drugs could be used to prevent and treat various inflammatory diseases.

2. Types of inflammasomes: structure and activation

Inflammasomes are protein complexes that trigger inflammatory responses in macrophages by the proteolytic activation of caspase-1, an inflammatory caspase. This process results in GSDMD-mediated pyroptosis and the secretion of IL-1β and IL-18 [8–11,18,19]. On stimulation by different types of PAMPs, DAMPs, and other molecules, intracellular PRRs are activated and assemble inflammasome complexes. These complexes can be assembled with or without adaptor proteins such as apoptosis-associated speck-like protein containing caspase recruitment domain (CARD) (ASC) and pro-caspase-1 [8–11,18]. Inflammasomes are categorized into two

groups, canonical inflammasomes and noncanonical inflammasomes. Canonical inflammasomes are protein complexes consisting of NLRs (e.g., NLRP1, NLRP3, and NLRC4) or non-NLRs (e.g., AIM2, adaptor protein, ASC, and pro-caspase-1) [8,9,18,19]. In contrast, noncanonical inflammasomes are protein complexes consisting of inflammatory caspases such as caspase-11 in mice or caspase-4 and caspase-5 in humans and intracellular lipopolysaccharide (LPS) [10,11]. While canonical and noncanonical inflammasomes assemble complexes after activation by different stimuli, they work in a similar way during macrophage-mediated inflammatory responses by activating caspase-1. This activation leads to GSDMD-mediated pyroptosis and the secretion of IL-1β and IL-18 [8–11,18].

Canonical inflammasomes are classified based on the names of their cognate PRRs. NLRP1 inflammasomes consist of NLRP1 and pro-caspase-1 (Fig. 1A) [8,9,18,19]. NLRP1 was identified as the first member of the NLR family [32] and has an N-terminal pyrin domain (PYD), a nucleotide-binding and oligomerization domain (NACHT), LRRs, a functional-to-find domain, and a C-terminal CARD (Fig. 1A). Whereas only one form of NLRP1 has been identified in humans, three isoforms (NLRP1A, NLRP1B, and NLRP1C) have been identified in mice. The N-terminal PYD motif present in human NLRP1 is absent in the mouse NLRP1 isoforms (Fig. 1A) [18]. On stimulation with the *Bacillus anthracis* toxin, NLRP1 inflammasomes are assembled by the direct interaction between NLRP1 and pro-caspase-1 through their CARD motifs (Fig. 1A) [33]. NLRP1 was shown to have a critical role in preventing pyroptosis and the secretion of IL-1β and IL-18 from macrophages from *Nlrp1* knockout mice [33,34].

NLRP3 inflammasomes consist of NLRP3, ASC, and pro-caspase-1 (Fig. 1B) [8,9,18]. NLRP3 has an N-terminal PYD motif, a NACHT domain, and C-terminal LRRs (Fig. 1B). NLRP3 is activated by a variety of agents such as bacteria, protozoans, viruses, fungi, pore-generating toxins, hyaluronan, extracellular adenosine triphosphate (ATP), nucleic acid hybrids, β-amyloids, uric acid, alum, and silica. On stimulation by these agents, NLRP3 inflammasomes are assembled by the direct interaction between NLRP3 and ASC through their PYD motifs, leading to an interaction with pro-caspase-1 through their CARD motifs (Fig. 1B) [19,35].

Similarly, NLRC4 inflammasomes consist of NLRC4 and pro-caspase-1. NLRC4 has an N-terminal CARD domain, a NACHT domain, and C-terminal LRRs (Fig. 1C). The structure of NLRC4 is similar to that of NLRP3, but unlike NLRP3, it has a CARD motif instead of a PYD motif at the N-terminus (Fig. 1B and 1C). NLRC4 is activated by bacterial components such as bacterial flagellin and
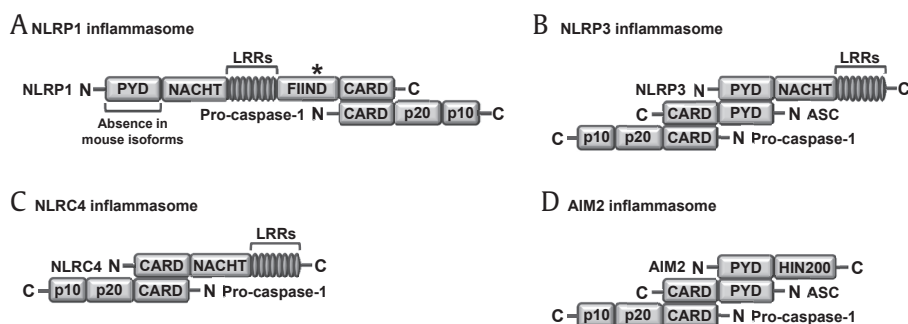

Fig. 1. **Structures of canonical inflammasomes.** (A) NLRP1 directly binds to pro-caspase-1 through their CARD motifs without the help of the adaptor molecule ASC. The N-terminal CARD motif is absent in the mouse NLRP1 isoforms. (B) Binding of NLRP3 to pro-caspase-1 is mediated by ASC. NLRP3 directly binds to ASC through their PYD motifs, whereas pro-caspase-1 directly binds to ASC through their CARD motifs. (C) NLRC4 directly binds to pro-caspase-1 through their CARD motifs without the help of the adaptor molecule ASC. (D) The binding of AIM2 to pro-caspase-1 is mediated by ASC. AIM2 directly binds to ASC through their PYD motifs, whereas pro-caspase-1 directly binds to ASC through their CARD motifs.
AIM2, absent in melanoma 2; ASC, apoptosis-associated speck-like protein containing caspase recruitment domain; CARD, caspase recruit domain; caspase, cysteine aspartate–specific protease; FIIND, function-to-find domain; NACHT, nucleotide binding and oligomerization domain; NLR, nucleotide-binding oligomerization domain-like receptor; LRR, leucine-rich repeat; PYD, pyrin domain.
*Autocatalytic cleavage.

bacterial needle subunits [36−41]. On stimulation by these ligands, NLRC4 inflammasomes are assembled by the direct interaction of NLRC4 and pro-caspase-1 through their CARD motifs (Fig. 1C).

AIM2 is a member of the p200 protein family and was initially identified as a direct sensor of intracellular double-stranded nucleic acids derived from pathogens. This sensor is another type of intracellular PRR that does not belong to an NLR inflammasome family [42]. AIM2 inflammasomes consist of AIM2, ASC, and pro-caspase-1; AIM2 has an N-terminal PYD motif and a C-terminal hematopoietic interferon-inducible nuclear protein domain (Fig. 1D). AIM2 is activated by intracellular double-stranded nucleic acids of various pathogens, such as *Francisella tularensis*, cytomegalovirus, and vaccinia virus. In response to these ligands, AIM2 inflammasomes are assembled in a similar manner as NLRP3 inflammasomes, i.e., direct interaction of AIM2 and ASC through their PYD motifs, leading to a subsequent interaction with pro-caspase-1 through their CARD motifs (Fig. 1D) [43−45].

Noncanonical inflammasomes were identified by the unexpected result that caspase-1 activation, pyroptosis, and secretion of IL-1β and IL-18 were not induced in macrophages derived from the 129S6 mouse strain. These mice express nonfunctional caspase-11 due to a polymorphism in the *caspase-11* gene locus [46]. This result suggested that caspase-11 forms another type of inflammasome that is distinct from canonical inflammasomes, hence its classification as a noncanonical inflammasome. Caspase-11 inflammasomes are assembled by direct binding of caspase-11 to a lipid A moiety of intracellular LPS derived from gram (−) bacteria, such as *Escherichia coli*, *Legionella pneumophilia*, *Citrobacter rodentium*, *Salmonella typhimurium*, *Shigella flexneri*, and *Burkholderia* spp. [10,11,47−54], through its CARD motif (Fig. 2A) [55]. Caspase-4

and caspase-5 are considered to be human homologs of mouse caspase-11 because they also bind directly to a lipid A moiety of gram (−) bacteria−derived intracellular LPS through their CARD motifs (Fig. 2A) [10,55−57]. After caspase-4/5/11 binds to intracellular LPS, it is subsequently activated by forming an oligomer complex through homologous interactions of its CARD motifs (Fig. 2B) [10,11,58].

Therefore, although different types of intracellular PRRs and their cognate ligands are involved, activation of both canonical and noncanonical inflammasomes results in the activation of caspase-1, a downstream effector molecule. This activation leads to GSDMD-mediated pyroptosis and the secretion of IL-1β and IL-18 during macrophage-mediated inflammatory responses. The inflammasomes discussed in this section are summarized in Table 1.

3. Roles of ginsenosides in inflammasome activation

Ginseng is a slow-growing perennial plant cultivated in Northeast America and East Asia. Ginseng has been used as an herbal medicine for thousands of years to ameliorate a variety of disease conditions, including fatigue, depression, aging, hypertension, gastric ulcer, stress, diabetes, and cancer [20−22,59]. In addition to its effects on these disease conditions, the effects of ginseng on inflammatory responses have been extensively explored [25,60,61]. An inflammatory response mediated mainly by myeloid immune cells (such as macrophages) is a host defensive innate immune response against invading pathogens. A number of studies have reported that inflammasomes play critical roles during inflammatory responses. Therefore, the roles of ginseng and ginseng-derived components in the activation of inflammasomes during

A Caspase-4/5/11 inflammasomes
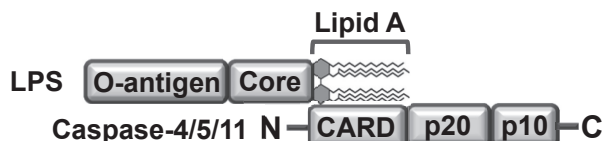
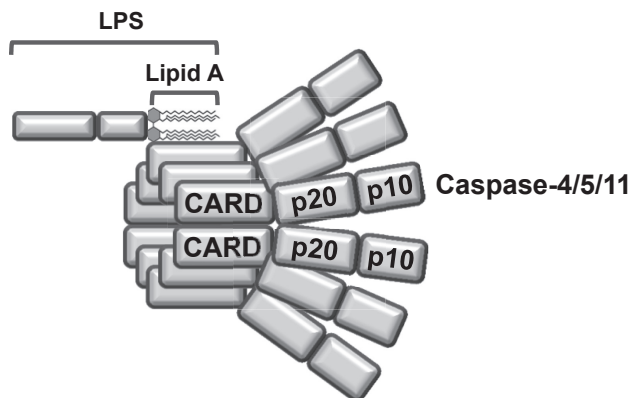### B Oligomerization of caspase-4/5/11 inflammasomes

Fig. 2. Structures of noncanonical inflammasomes. (A) Mouse caspase-11 and human caspase-4/5 directly bind through their CARD motifs and the lipid A moieties of intracellular LPS derived from Gram (−) bacteria. (B) Caspase-4/5/11 and LPS complexes are activated by oligomerization. Oligomerization involves binding of the caspase-4/5/11 molecules through their CARD motifs.
CARD, caspase recruit domain; caspase, cysteine aspartate−specific protease; LPS, lipopolysaccharide.

inflammatory responses have been investigated. These ginseng-derived components include various types of ginsenosides, which are pharmacologically active glycosides found in ginseng.

Korean Red Ginseng is a dark red steam-processed ginseng which has been reported to exhibit various biological activities, such as antiinflammatory, antioxidative, immune-enhancing, and anticancer activities [62−65]. Korean Red Ginseng has also been shown to affect the activation of inflammasomes during inflammatory responses. For instance, Kim et al prepared Korean Red Ginseng extract (RGE) and demonstrated its effects on the activation of inflammasomes both *in vitro* and *in vivo*, i.e., in human macrophages and in mice. Moreover, RGE markedly suppressed the activation of NLRP3 and AIM2 inflammasomes, resulting in the suppression of macrophage pyroptosis and the maturation/secretion of IL-1β in *in vitro* and *in vivo* models [66]. Further studies aimed to identify the compounds in RGE that are responsible for this inhibition of inflammasome activation; two ginsenosides, Rh1 (Fig. 3A) and Rg3 (Fig. 3B), were found to inhibit the secretion of IL-1β by macrophages in a dose-dependent manner [66]. These results suggest that the ginsenosides Rh1 and Rg3, which are found in RGE, play a critical role in preventing pyroptosis and the maturation/secretion of IL-1β. These effects are mediated by suppressing the activation of the NLRP3 and AIM2 inflammasomes during macrophage-mediated inflammatory responses.

Rg3 is a tetracyclic triterpenoid saponin which is abundant in red ginseng [67]. Studies have investigated the molecular mechanism by which the ginsenoside Rg3 inhibits inflammasome activation in macrophages. Rg3 was shown to effectively decrease the production of nitric oxide (NO) and reactive oxygen species and to downregulate the expression of inducible nitric oxide synthase. These effects lead to the inhibition of NLRP3 inflammasome activation by blocking NO-induced NLRP3 *S*-nitrosylation in macrophages [68]. Moreover, Rg3 was shown to attenuate death due to LPS-induced endotoxic shock in mice by decreasing apoptotic cell death in the spleen and inducible nitric oxide synthase expression and NO production in the spleen and the liver [68]. This study suggests that ginsenoside Rg3, a major bioactive constituent of ginseng, could act as an antiinflammatory therapeutic agent for the treatment of inflammatory diseases (including sepsis) by deactivating inflammasomes during inflammatory responses.

The inhibitory effects of ginsenosides on inflammasome activation have also been investigated during inflammatory responses in adipose tissues. Exposure to chronic cellular stresses or metabolic disease induces endoplasmic reticulum stress and initiates inflammatory responses in specialized tissues, including adipose tissue [69,70]. Rb1 (Fig. 3C) and compound K (Fig. 3D) are natural tetracyclic triterpene saponins found exclusively in ginseng [71]. Chen et al reported that two ginsenosides, Rb1 and compound K, suppressed the activation of NLRP3 inflammasomes in adipocytes. This suppression resulted in the inhibition of IL-1β maturation and IL-6 secretion [72]. Moreover, the two ginsenosides were shown to ameliorate insulin resistance, which is characterized by impaired insulin signaling [72]. This impaired signaling is induced by inflammatory responses in adipocytes [73].

Another ginseng compound, chikusetsu saponin IVa (CS IVa) (Fig. 3E), was also shown to suppress inflammasome activation in inflammatory adipose tissue from high-fat diet (HFD)−fed mice. CS IVa is an oleanane-type pentacyclic triterpene saponin found in some medicinal plants, including ginseng and *Aralia taibaiensis* [74,75]. CS IVa has been shown to significantly reduce inflammatory responses and the expression of NLRP3 inflammasome components (e.g., IL-1β, caspase-1, NLRP3, and ASC) in adipose tissue isolated from HFD-fed mice [76]. Moreover, CS IVa was shown to inhibit the activation of NLRP3 inflammasomes and NLRP3-mediated formation of ASC pyroptosomes, leading to suppression of LPS-induced pyroptosis in macrophages [76].

The effect of Rg5 (Fig. 3F) on inflammasome activation in adipose tissue has also been investigated. Rg5 is a tetracyclic
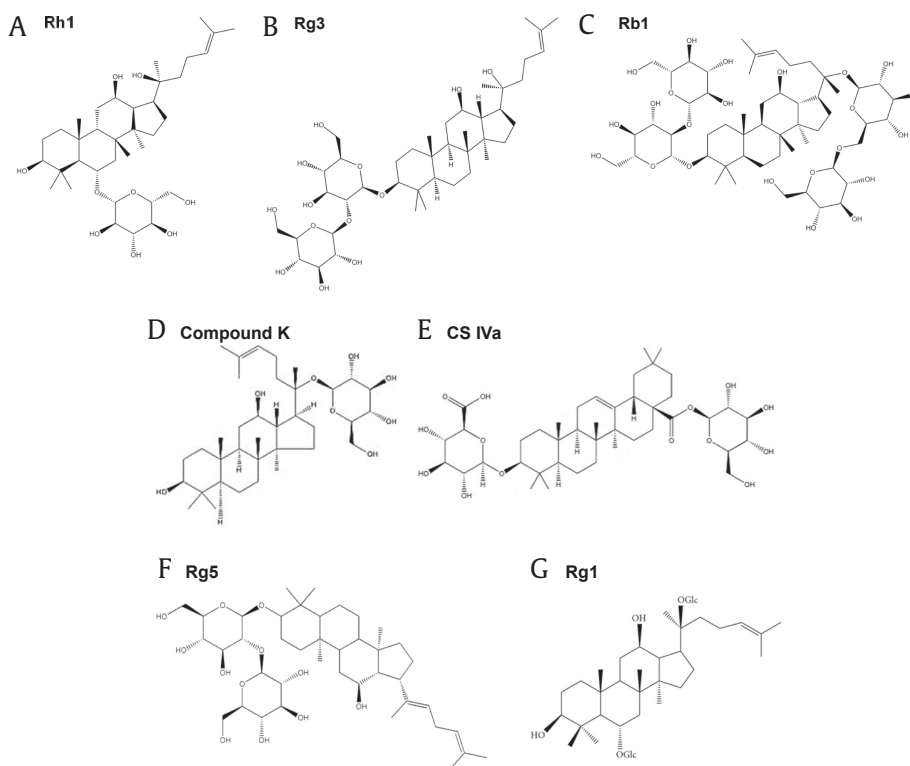

Fig. 3. Chemical structures of ginsenosides. (A) Rh1. (B) Rg3. (C) Rb1. (D) Compound K. (E) CS IVa. (F) Rg5. (G) Rg1. CS IVa, chikusetsu saponin IVa.

Table 1
Structures and activation of inflammasomes

Groups	Classes	Motifs	Components	Ligand(s)	Ref.
Canonical inflammasomes	NLRP1	CARD, FIIND, LRRs, NACHT, and PYD	NLRP1 and pro-caspase-1	*Bacillus anthracis* toxin	[1−7]
	NLRP3	LRRs, NACHT, and PYD	NLRP3, ASC, and pro-caspase-1	Bacteria, protozoans, viruses, fungi, pore-generating toxins, hyaluronan, extracellular ATP, nucleic acid hybrids, β-amyloids, uric acid, alum, and silica	[1−4,8]
	NLRC4	LRRs, NACHT, and CARD	NLRC4 and pro-caspase-1	Bacterial flagellin and bacterial needle subunits	[9−14]
	AIM2	PYD and NIH200	AIM2, ASC, and pro-caspase-1	Intracellular double-stranded nucleic acids	[15−18]
Noncanonical inflammasomes	Caspase-4/5/11	CARD, p20, and p10	Caspase-4/5/11 and LPS	Intracellular LPS	[19−28]

AIM2, absent in melanoma 2; ASC, apoptosis-associated speck-like protein containing caspase recruitment domain; CARD, caspase recruit domain; Caspase, cysteine aspartate−specific protease; FIIND, function-to-find domain; LPS, lipopolysaccharide; LRR, leucine-rich repeat; NACHT, nucleotide binding and oligomerization domain; NLR, nucleotide-binding oligomerization domain-like receptor; PYD, pyrin domain.

triterpenoid saponin and a main, yet rare, saponin generated during ginseng steaming [77]. Rg5 has been shown to suppress the activation of NLRP3 inflammasomes and to suppress lipolysis in adipose tissue of HFD-fed mice, thereby inhibiting adipose dysfunction and insulin resistance [78].

A recent study explored the suppressive effect of a ginsenoside on inflammasome activation during atherosclerosis pathogenesis. Atherosclerosis is an inflammatory disease in which plaque accumulates inside the arteries. Zhou et al reported that compound K prevents the accumulation of atherosclerotic plaque and suppresses inflammasome activity by reducing the protein levels of NLRP3, mature IL-1β, and caspase-1 in the atherosclerotic lesions of ApoE$^{−/−}$ mice [79]. Moreover, compound K was shown to significantly decrease the protein levels of NLRP3 inflammasome components (e.g., NLRP3, mature IL-1β, and caspase-1) in macrophages isolated from ApoE$^{−/−}$ mice [79].

Another recent study examined the suppressive effect of Rg1 (Fig. 3G) on inflammasome activation in the generation and progression of Alzheimer's disease, a chronic neurodegenerative disease, using a mouse model. Rg1 is a tetracyclic triterpenoid saponin and a major bioactive ingredient of *Panax ginseng* [80]. Rg1 exerted neuroprotective activity against glucocorticoid-induced neuroinflammation damage in the brains of glucocorticoid-injected mice. Specifically, Rg1 suppressed behavioral defects and alleviated neuronal degeneration [81]. Interestingly, this suppressive effect of Rg1 against neuroinflammatory damage was achieved by inhibiting NLRP1 inflammasome activation. Rg1 significantly downregulated the expression of NLRP1 inflammasome components (e.g., ASC and pro-caspase-1) and inflammasome-specific proinflammatory cytokines (e.g., IL-1β and IL-18) in the hippocampus of glucocorticoid-injected mice [81].

Taken together, these results strongly suggest that ginseng and various ginseng-derived ginsenosides (e.g., Rh1, Rg3, CS IVa, Rg5, Rb1, compound K, and Rg1) play a protective role during the pathogenesis of various inflammatory diseases by inhibiting the activation of inflammasomes and their downstream effector components, as summarized in Table 2.

4. Conclusion

Inflammation is a host defense mechanism mediated by innate immune cells. This mechanism involves the recognition of PAMPs and DAMPs by PRRs, which are expressed on the surface of inflammatory cells or intracellularly within the inflammatory cells. A hallmark of inflammatory responses is the activation of inflammasomes, which are intracellular protein complexes. On stimulation by different types of ligands, intracellular PRRs such as NLRs

Table 2
Roles of ginsenosides in the activation of inflammasomes

Ginsenosides	Targets	Mode of actions	Models	Ref.
Rh1	NLRP3 & AIM2	Suppressor	Human and mouse macrophages Mice	[29]
Rg3	NLRP3 & AIM2	Suppressor	Human and mouse macrophages Mice	[29]
	NLRP3	Suppressor	Mouse macrophages Human keratinocytes Mice	[29,30]
Rb1	NLRP3	Suppressor	Mouse adipocytes Mouse adipose tissues	[31]
Compound K	NLRP3	Suppressor	Mouse adipocytes Mouse adipose tissues	[31,32]
		Suppressor	Mouse macrophages Mice	[31,32]
CS IVa	NLRP3	Suppressor	Mouse adipose tissues Mouse macrophages	[33]
Rg5	NLRP3	Suppressor	Mouse adipocytes	[34]
Rg1	NLRP1	Suppressor	Mice	[35]

AIM2, absent in melanoma 2; CS IVa, chikusetsu saponin IVa; NLR, nucleotide-binding oligomerization domain-like receptor.

and AIM2 are activated. This activation results in the assembly of canonical inflammasome complexes, which consist of an intracellular PRR and pro-caspase-1. These complexes may or may not contain the adaptor molecule ASC. Intracellular caspases 4/5/11 also directly recognize intracellular LPS derived from gram (−) bacteria and are activated by assembling noncanonical inflammasome complexes, which consist of caspase-4/5/11 and LPS. The activation of inflammasomes subsequently activates their downstream effector, caspase-1, resulting in GSDMD-mediated pyroptosis and the secretion of proinflammatory cytokines such as IL-1β and IL-18. Many types of ginsenosides, steroid glycosides, and triterpene saponins have been identified as active components that exhibit various biological functions, including antiinflammatory actions. Moreover, some types of ginsenosides have been reported to have antiinflammatory activities by suppressing the activation of several types of inflammasomes (e.g., NLRP3, NLRP1, and AIM2 inflammasomes) during inflammatory responses. Moreover, these ginsenosides have been shown to effectively inhibit the activation of caspase-1 and to reduce the expression of IL-1β and IL-18. Given the results discussed in the present review, ginsenosides play a critical role in suppressing the activation of various inflammasomes

during inflammatory responses. Overall, these results strongly suggest that targeting inflammasomes using ginsenoside-containing therapeutics could be a novel and promising strategy for preventing and treating inflammatory diseases.

Conflicts of interest

The author has no conflicts of interest to declare.

Abbreviations

PAMP   Pathogen-associated molecular pattern
DAMP   Danger-associated molecular pattern
PRR   Pattern-recognition receptor
NLR   Nucleotide-binding oligomerization domain-like receptor
AIM2   Absent in melanoma 2
Caspase Cysteine aspartate−specific protease
GSDMD   Gasdermin D
ASC   Apoptosis-associated speck-like protein containing CARD
LPS   Lipopolysaccharide
PYD   N-terminal pyrin domain
NACHT   Nucleotide-binding and oligomerization domain
LRR   Leucine-rich repeat
FIIND   Functional-to-find domain
CARD   C-terminal caspase recruit domain
HIN   Hematopoietic interferon-inducible nuclear protein
IL   Interleukin

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