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Review Article

Regulatory roles of ginseng on inflammatory caspases, executioners of inflammasome activation

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ABSTRACT

Inflammation is an immune response that protects against pathogens and cellular stress. The hallmark of inflammatory responses is inflammasome activation in response to various stimuli. This subsequently activates downstream effectors, that is, inflammatory caspases such as caspase-1, 4, 5, 11, and 12. Extensive efforts have been made on developing effective and safe anti-inflammatory therapeutics, and ginseng has long been traditionally used as efficacious and safe herbal medicine in treating various inflammatory and inflammation-mediated diseases. Many studies have successfully shown that ginseng plays an anti-inflammatory role by inhibiting inflammasomes and inflammasome-activated inflammatory caspases. This review discusses the regulatory roles of ginseng on inflammatory caspases in inflammatory responses and also suggests new research areas on the anti-inflammatory function of ginseng, which provides a novel insight into the development of ginseng as an effective and safe anti-inflammatory herbal medicine.

1. Introduction

Inflammation is an innate immune response that protects the body against microbial infection and cellular stress and is characterized by five hallmarks: redness, swelling, heat, pain, and loss of tissue functions [1–3]. The inflammatory response is initiated through recognizing pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs) by pattern recognition receptors (PRRs) expressed on or in inflammatory cells [1,2,4]. The inflammatory response consists of two main consecutive steps: priming and triggering. Priming is a preparatory step in activating intracellular signal transduction cascades in inflammatory pathways, such as nuclear factor-kappa B (NF-κB), activator protein-1, and interferon regulatory factors, resulting in inflammatory gene expression and inflammatory mediator generation [5–7]. By contrast, triggering is the boosting step in activating inflammasomes, protein complexes comprising intracellular PRRs, and inflammatory molecules, resulting in gasdermin D (GSDMD)–mediated pyroptosis, an inflammatory cell death via forming membrane GSDMD pores, as well as the caspase-1–mediated maturation and secretion of proinflammatory cytokines, interleukin (IL)-1β, and IL-18, through the GSDMD pores [8–13].

Cysteine–aspartic proteases (caspases) are a family of endoproteases that hydrolyze the substrates after aspartic acid residues with their specific cysteine protease activity [14]. Caspases consist of an N-terminal caspase recruitment domain (CARD; caspase-1, 2, 4, 5, 9, 11, and 12) or two N-terminal death effector domains (DED; caspase-8 and 10), sequentially followed by large (~20 kDa) and small (~10 kDa) catalytic domains. However, executioner caspases, such as caspase-3, 6, 7, and 14, lack both CARD and DED and have only large and small catalytic domains. Caspases are initially generated as inactive zymogens (procaspases), and caspases are activated by proteolytic cleavage of dimeric or often oligomeric

Abbreviations: AIM2, Absent in melanoma 2; ASC, Apoptosis-associated speck-like protein containing CARD; Caspase, *Cysteine aspartate*–specific protease; CARD, C-terminal caspase recruit domain; COX-2, Cyclooxygenase-2; DAMP, Danger-associated molecular pattern; FIIND, Functional-to-find domain; GSDMD, Gasdermin D; HIN, Hematopoietic interferon-inducible nuclear protein; IL, Interleukin; LPS, Lipopolysaccharide; LRR, Leucine-rich repeat; NACHT, Nucleotide-binding and oligomerization domain; NO, Nitric oxide; NLR, Nucleotide-binding oligomerization domain-like receptor; NF-κB, Nuclear factor-kappa B; PGE_2, Prostaglandin E_2; PAMP, Pathogen-associated molecular pattern; PRR, Pattern-recognition receptor; PYD, N-terminal pyrin domain; RGE, Korean Red Ginseng; ROS, Reactive oxygen species.

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procaspases into large and small subunits in response to specific stimuli, followed by the molecular interaction of these subunits to form active homodimeric or heterodimeric caspases. Historically, caspases were identified as inducers of apoptosis, a form of programmed cell death that removes old and injured cells [15]. Interestingly, recent studies identified new types of caspases involved in inflammatory responses, named as inflammatory caspases, and have uncovered the molecular mechanisms by which these inflammatory caspases induce pyroptosis, an inflammatory cell death that promotes the secretion of proinflammatory cytokines, IL-1β, and IL-18 [16]. Accumulating evidence has shown that dysregulation of caspase functions in biological processes is strongly associated with inflammation, autoimmunity, tumorigenesis, and infectious pathologies [17–19].

Panax ginseng (Korean ginseng) is a perennial slow-growing plant that is cultivated mostly in the East Asian and North American countries. Ginseng has long been used as traditional herbal medicine as itself or in combination with other medicines to treat various human diseases, including cancers, diabetes, hypertension, stroke, cardiovascular, neurodegenerative, infectious, and inflammatory diseases [20–29]. Similar to other plants, ginseng comprises four main parts: berries, leaves, stalks, and roots, but the general term ginseng indicates its roots. Because ginseng contains much water, it is easily decaying at room temperature; therefore, it is often processed to red ginseng by repeated steaming and drying. Studies have shown that red ginseng contains higher contents of bioactive compounds showing better biological activity and lower adverse effects compared with fresh ginseng [30]. Many efforts have been made on identifying the constituents in ginseng, and it has been reported that ginseng contains various bioactive compounds, including ginsenosides, alkaloids, glucosides, polysaccharides, and polypeptides exerting antiaging, antidiabetic, immunoregulatory, neuroregulatory, anticancer, lipid-regulatory, and antithrombotic activities [31]. Of these, ginsenosides are the major constituents in ginseng. Ginsenosides are a class of natural steroidal glycosides and triterpenoid saponin, and >100 different types of ginsenosides have been identified, of which many have been characterized to date. Based on their structures, ginsenosides are classified into three main types: protopanaxadiol (PPD), protopanaxatriol, and rare ginsenosides. Different reactive groups and molecules are linked to different sites of the ginsenoside backbone, resulting in the generation of various distinct ginsenosides. As major bioactive compounds in ginseng, ginsenosides have been shown to have pharmacological activities in alleviating symptoms of various human diseases, including cancer, diabetes, cardiovascular diseases, neurological, inflammatory, and autoimmune diseases [21,28,29,32–36].

This review aims to summarize and discuss recent research progress in understanding the regulatory roles of ginseng on the functions of inflammatory caspases, downstream effectors of inflammasome activation during inflammatory responses. Moreover, this review highlights the potential of ginseng as an anti-inflammatory agent to provide future insight into the development of efficacious and safe complementary and alternative medicines to prevent and treat various human diseases.

2. Inflammatory caspases

Caspases induce apoptotic cell death by playing as either initiators (caspase-2, 8, 9, and 10) or executioners (caspase-3, 6, and 7), and these caspases play critical roles in promoting apoptotic cell death in response to various stimuli. Cell death was also observed in macrophages infected with the gram-negative bacteria, *Shigella flexneri* or *Salmonella typhimurium* [37,38]. Interestingly, the features of this type of cell death were distinct from those of apoptosis and later characterized as a novel type of cell death induced by inflammatory responses, now known as pyroptosis [39,40]. Similar to apoptosis, caspases are actively involved in pyroptosis, whereas caspases functioning in pyroptosis are different from caspases involved in apoptosis; therefore, these caspases that play roles in innate immune responses are named as “inflammatory caspases.” Pyroptosis is the cell death process induced by inflammatory responses to dispose pathogen-laden macrophages and clear infected intracellular pathogens in response to a variety of PAMPs and DAMPs. Pyroptosis involves the activation of inflammasomes, intracellular protein complexes, comprising intracellular PRRs and inflammatory molecules, and inflammatory caspases, leading to cell lysis due to GSDMD-mediated membrane pore formation and water influx–mediated osmotic pressure, followed by the secretion of proinflammatory cytokines, IL-1β and IL-18 [10,39,41,42]. Several types of inflammatory caspases have been identified (Fig. 1) and demonstrated to play a pivotal role in inflammasome activation pathways during inflammatory responses.

2.1. Caspase-1

Several types of novel caspases have been identified in mammals to play a pivotal role in inflammatory responses. The first caspase identified as inflammatory caspase was caspase-1. Caspase-1 is found in both humans and mice, and despite the difference in amino acid length (human and mouse caspase-1; 404 and 402 amino acids, respectively), both consist of N-terminal CARD, a large catalytic subunit (p20), and C-terminal small catalytic subunit (p10) (Fig. 1). The first indication of the functional involvement of caspases in inflammatory responses was reported by the discovery of caspase-1 to facilitate the proteolytic processing and maturation of IL-1β and IL-18 cytokines, critical inflammatory mediators [43,44]. Proteolytic maturation of inactive pro-IL-1β and pro-IL-18 and secretion of mature active IL-1β and IL-18 were defective in caspase-1-deficient mice, which were more resistant to endotoxin lipopolysaccharide (LPS)-induced septic shock [45,46] and intestinal inflammation [47]. Caspase-1 is activated by associating with multiple canonical nucleotide-binding and oligomerization domain-like receptor (NLR) family (NLRP1, NLRP3, and NLRC4) or absent in melanoma 2 (AIM2) inflammasomes in response to inflammasome-stimulating ligands. Recruitment of the inactive caspase-1 to these canonical inflammasomes with or without the help of a bipartite adapter, apoptosis-associated speck-like protein (ASC), results in the proteolytic cleavage of caspase-1, which is activated by forming a homodimer of processed p20–p10 subunits [8,10]. The active caspase-1 subsequently induces the proteolytic cleavage of GSDMD, and the cleaved N-terminal GSDMD fragments move to the cell membrane and generate the GSDMD pores, resulting in pyroptosis. The active caspase-1 also induces the proteolytic maturation of active IL-1β and IL-18, and these active proinflammatory cytokines are secreted through the GSDMD pores (Fig. 2).

2.2. Caspase-11

After the discovery of caspase-1 as an inflammatory caspase, other types of caspases have been further identified in mammals [48,49]. Bacterial toxins have been shown to induce inflammatory responses in macrophages by activating inflammasome pathways, leading to IL-1β secretion. Unexpectedly, NLRP3 inflammasome activation and subsequent IL-1β secretion induced by cholera toxin B have been observed to be abolished in bone marrow–derived macrophages (BMDMs) isolated from the 129S6 mouse strain that expresses the truncated and nonfunctional caspase-11 due to polymorphisms in the *caspase-11* gene locus [48]. In addition, these

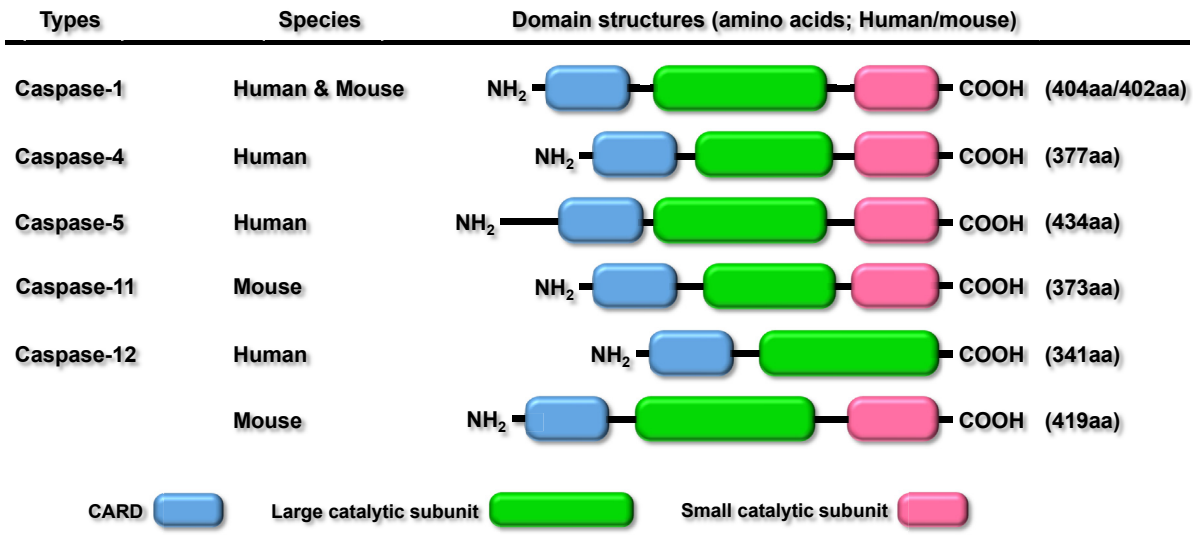

Fig. 1. Structures of human and mouse inflammatory caspases. The members of the inflammatory caspases are caspase-1, 4, 5, 11, and 12 in humans and mice. These inflammatory caspases share an N-terminal CARD, a large catalytic subunit (p20), and a C-terminal small catalytic subunit (p10). Unlike other caspases, human caspase-12 consists of only an N-terminal CARD and a C-terminal large catalytic subunit (p20) and does not have a small catalytic subunit (p10). Phylogenetically and structurally, mouse caspase-12 belongs to an inflammatory caspase family. CARD, caspase recruitment domain.

mice were also much more resistant to septic shock induced by a lethal dose of LPS, an endotoxin in the outer membrane of gram-negative bacteria [48]. A series of follow-up studies have further shown that caspase-11-induced inflammatory responses are activated by gram-negative bacterial infection [50–52], suggesting that caspase-11 is a novel inflammatory caspase not yet identified as a component involved in the canonical inflammasome pathway and plays a unique role during the inflammatory responses in macrophages. Moreover, the molecular mechanism by which caspase-11 induces inflammatory responses in macrophages is different from that of canonical inflammasome pathways; therefore, caspase-11-mediated inflammatory responses were described as a "noncanonical inflammasome" pathway [53–55]. Similar to caspase-1, caspase-11 comprises an N-terminal CARD, a large catalytic subunit (p20), and a C-terminal small catalytic subunit (p10), with a length of 373 amino acids (Fig. 1). Caspase-11 directly interacts with intracellular LPS, and LPS–caspase-11 complexes are oligomerized to form the caspase-11 noncanonical inflammasome in macrophages infected with gram-negative bacteria [53–55]. Subsequently, the caspase-11 noncanonical inflammasome cleaves GSDMD at the aspartic acid residue at the 276t0h position (Asp^{276}) to produce N-terminal and C-terminal GSDMD fragments, and the cleaved N-terminal GSDMD fragments move to the cell membrane, followed by GSDMD pore production, leading to pyroptosis (Fig. 2). The caspase-11 noncanonical inflammasome also promotes caspase-1 function by activating the NLRP3 inflammasome. The underlying mechanism by which caspase-11 noncanonical inflammasome activates NLRP3 inflammasome is still poorly understood; however, some studies reported that K^+ efflux, an essential and sufficient process for NLRP3 inflammasome activation, is induced during inflammatory responses [56,57]. Another study also reported that N-terminal GSDMD fragments produced by caspase-11 noncanonical inflammasome activate NLRP3 inflammasome in macrophages [58]. Caspase-1 activated by caspase-11 noncanonical inflammasome facilitates the proteolytic maturation of the inactive pro-IL-1β and pro-IL-18 to produce active IL-1β and IL-18, and these proinflammatory cytokines are secreted through the GSDMD pores.

2.3. Caspase-4/5

Caspase-11 was initially discovered in mice; however, human caspases with similar functions with mouse caspase-11 in inflammatory responses were not found. Therefore, many efforts have been made in identifying the human homologs of mouse caspase-11. Similar to mouse caspase-11, human caspase-4 and 5 reportedly directly interacts with LPS derived from gram-negative bacteria, followed by the formation of the oligomeric caspase-4/5 noncanonical inflammasome, leading to pyroptosis [49]. Similar to other inflammatory caspases, human caspase-4/5 also comprise an N-terminal CARD, a large catalytic subunit (p20), and a C-terminal small catalytic subunit (p10) (Fig. 1). However, their sizes are quite different, and caspase-4 and 5 are 377 and 434 amino acids in length, respectively, (Fig. 1). Recent studies have further shown that caspase-4/5 noncanonical inflammasomes induced the proteolytic activation of GSDMD and caspase-1 by direct interaction between caspase-4/5 and intracellular LPS, leading to pyroptosis by GSDMD-mediated pore formation and caspase-1-promoted maturation and IL-1β and IL-18 secretion through GSDMD pores (Fig. 2) [49,59–64]. Differences in functions might exist between mouse caspase-11 and human caspase-4/5 during inflammatory responses, which has not been demonstrated yet; however, evidence shows that caspase-4/5 are accepted as human counterparts of mouse caspase-11 that play a pivotal role in inflammasome-activated inflammatory responses by directly recognizing intracellular LPS.

2.4. Caspase-12

Caspase-12 is found in both humans and rodents. Functional full-length caspase-12 is expressed in rodents; however, caspase-12 exists in full length and truncated forms because of the alternative splicing in humans (Fig. 1) [65]. Caspase-12 is not expressed in 75% of the human population, including all Caucasians and most Africans, Americans, and Asians, whereas the remaining 25% population of North and sub-Saharan Africans express full-length caspase-12 with proteolytically inactive pseudoprotease activity

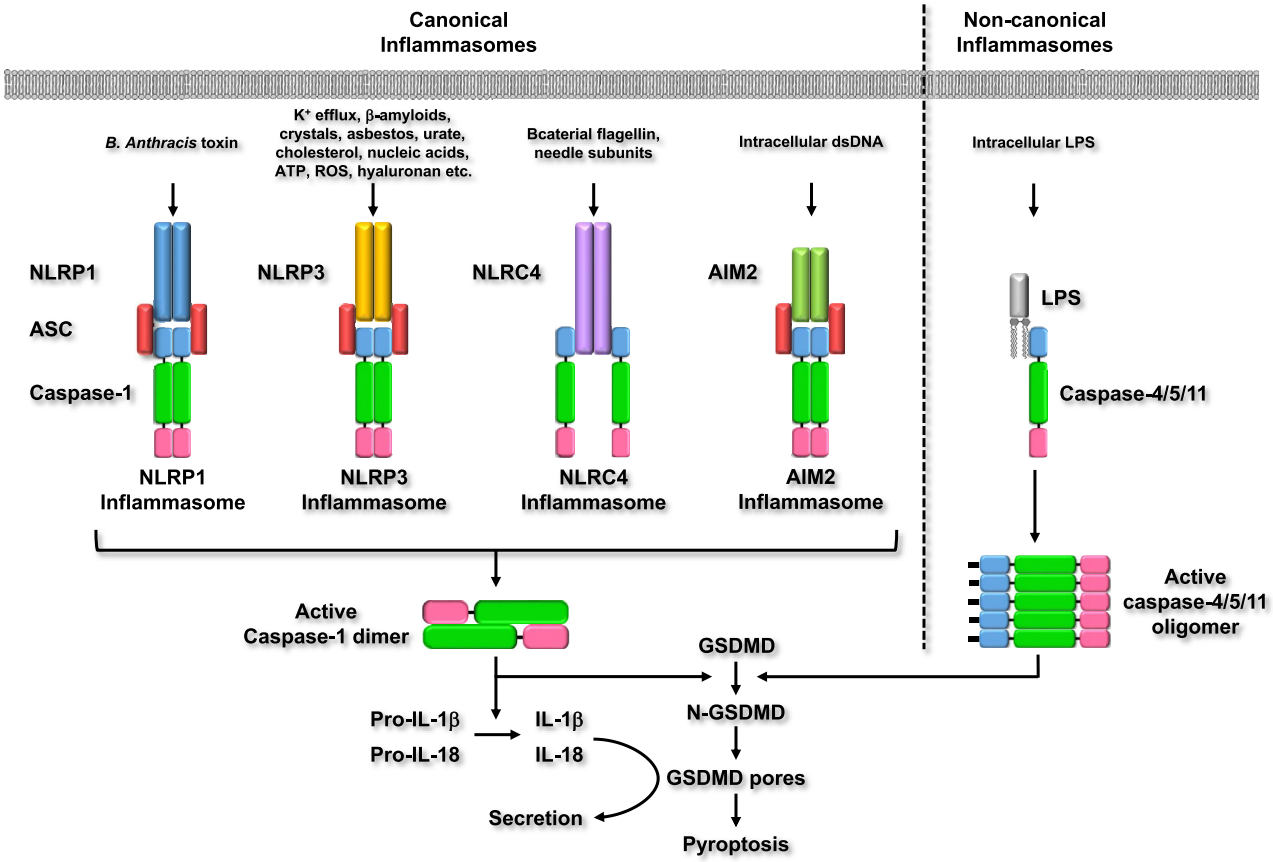

Fig. 2. Roles of the inflammatory caspases in inflammasome-activated inflammatory responses. Canonical inflammasomes, such as NLRP1, NLRP3, NLRC4, and AIM2 inflammasomes assemble in response to their specific ligands, leading to proteolytic activation of caspase-1 to form p20–p10 dimers. Caspase-4/5/11 noncanonical inflammasomes assemble by direct recognition of intracellular LPS, followed by oligomerization of LPS–caspase-4/5/11 complexes. Active caspase-1 and caspase-4/5/11 noncanonical inflammasomes, in turn, cleave GSDMD to produce N-terminal GSDMD fragments, and cleaved N-terminal GSDMD fragments move to the cell membrane, generate GSDMD pores, and induce pore-mediated pyroptosis. Active caspase-1 also maturates inactive pro–IL-1β and pro–IL-18 by proteolytic processing to produce active IL-1β and IL-18, which are secreted through GSDMD pores. NLR, nucleotide-binding and oligomerization domain-*like* receptor; AIM2, absent in melanoma 2; LPS, lipopolysaccharide; GSDMD, gasdermin D; IL, interleukin.

[65,66]. Caspase-12 belongs to the inflammatory caspase subfamily based on phylogenetic clustering [14]; however, the role of caspase-12 and molecules functionally interacting with caspase-12 has been poorly understood to date. Early studies suggested that caspase-12 plays a role in the endoplasmic reticulum (ER) stress-mediated apoptosis; however, the recent scientific consensus is that caspase-12 is not necessary for apoptosis. Population and *in vivo* studies using animal models of infectious diseases and sepsis have further shown the role of full-length caspase-12 in inflammatory responses. Interestingly, in contrary to other inflammatory caspases, caspase-12 acts as a negative regulator of inflammatory responses. Caspase-12 inhibits inflammatory responses by suppressing caspase-1 and IL-1β secretion, and this inhibitory function is independent on protease activity [67]. In addition, bacterial clearance and resistance to endotoxin-induced septic shock were also enhanced in mice deficient with the *caspase-12* gene, and the protease activity of caspase-12 was not required for this effect [68]. Moreover, decreased inflammatory and innate immune responses and enhanced susceptibility to sepsis were observed in ~20% of the sub-Saharan African population who expresses the full-length functional caspase-12 [69]. These studies strongly suggest that caspase-12 plays an anti-inflammatory role in inflammatory responses. By contrast, a recent study analyzing systemic canonical and noncanonical inflammasome responses in macrophages and animal models showed that caspase-12 deficiency suppressed inflammatory responses by abrogating caspase-11 expression and subsequently inhibiting noncanonical caspase-1 activation [70], suggesting that caspase-12 may possibly play a proinflammatory role in inflammatory responses. It is still unclear whether caspase-12 is an anti-inflammatory or a proinflammatory caspase because of a limited number of studies, and given the contradictory observations, further studies investigating the roles of caspase-12 in inflammatory responses are highly required.

3. Regulatory roles of ginseng on inflammatory caspases

3.1. *Effect on caspase-1*

Saponin, a natural glycoside with a wide range of pharmacological properties, is the major constituent in ginseng. Therefore, efforts have been made in isolating the saponins from ginseng and evaluating their effects on caspase-1 functions.

Li et al prepared total saponins of *Panax notoginseng* (TSPN) and evaluated the effect of TSPN on caspase-1 in rats with cerebral ischemia-reperfusion injury. Inflammation and oxidative stress interactively play critical roles in ischemia-reperfusion injury [71]. TSPN exhibits a neuroprotective effect by reducing caspase-1 expression, which is elevated in the brain tissue of rats with ischemia-reperfusion injury [72], indicating that the protective effect of TSPN on the neuroinflammatory disease is associated with the inhibition of inflammatory caspase-1 activation. A similar study conducted by Tang et al [73] investigated the effect of *Panax*

notoginseng saponins (PNS) on caspase-1 in the same disease by using a rat model. However, this study showed that PNS has no effect on caspase-1 expression, which is elevated in the brain tissue of rats with ischemia-reperfusion injury. Discrepant results may be because of the difference in the total contents of PNS used in the studies. In addition, different methods were used to generate the same cerebral ischemia-reperfusion injury model in rats. Li et al used a transient middle cerebral artery occlusion model [72], whereas Tang et al induced the disease by nylon monofilament via the internal carotid artery [73]. This methodological difference might produce different results. Aging is characterized by chronic low-grade inflammation with multiple diseases, and chronic and systemic inflammation induces aging-related cognitive deficits [74]. Ruan et al [75] investigated the effect of total saponins of Japanese ginseng, *Panax japonicas* (SPJ) on caspase-1 in natural aging rats with cognitive decline. SPJ improved the declined cognitive function in aging rats and decreased the damage of long-term potentiation in the brain of aging rats. Moreover, SPJ reduced caspase-1 expression in aging rats [75], indicating that SPJ could ameliorate cognitive decline induced by chronic inflammation during the aging process by inhibiting inflammatory caspase-1 expression. In accordance with the previous observation, ginseng saponins exhibit an anti-inflammatory effect, but it is noteworthy that ginseng saponin-suppressed inflammatory responses could be mediated by inhibiting inflammatory caspase-1, a critical effector in inflammatory responses.

Ginsenosides are saponins, and >100 ginsenosides have been discovered. Therefore, despite the suppressive effect of total ginseng saponins on caspase-1, efforts have been further made on identifying a single ginsenoside to show a caspase-1-inhibitory effect in inflammatory responses. Oh et al [76] identified ginsenoside Rg1 as a negative regulator of caspase-1 activation in the inflammatory disease, allergic rhinitis. Rg1 markedly reduced the symptoms and disease biomarkers in mice with ovalbumin-induced allergic rhinitis and also inhibited caspase-1 activation in the nasal mucosa tissue. These results suggest that Rg1 ameliorates allergic rhinitis by inhibiting inflammatory caspase-1. Yuan et al [77] identified Chikusetsu saponin IVa (Cs IVa) as one of the major components of Japanese ginseng, *Panax japonicas* that suppresses caspase-1 expression in the mice with high-fat diet (HFD)-induced inflammation. Cs IVa markedly improved HFD-induced lipid homeostasis and suppressed HFD-induced inflammation in the adipose tissues [77]. Cs IVa also shifted the polarization of adipose tissue macrophages from M1 to M2 and inhibited HFD-induced expression of inflammasome pathway components, NLRP3, ASC, IL-1β, and caspase-1 in both mice and BMDMs isolated from HFD-fed mice [77]. These results provide the evidence that Cs IVa effectively ameliorates HFD-induced inflammation in the adipose tissues in mice by inhibiting the activation of an NLRP3 inflammasome pathway, as well as caspase-1. Du et al [78] evaluated the neuroprotective effects of ginsenoside Rf in *P. notoginseng* on amyloid β (Aβ)—induced neuroinflammation and neurotoxicity. Rf ameliorated Aβ-induced inflammatory responses by down-regulating caspase-1 expression and facilitated Aβ clearance in the mouse neuroblastoma cell line, N2A cells transfected with mutant APP695. Moreover, Rf administration significantly improved memory and spatial learning in the Aβ-induced Alzheimer disease mouse model [78], indicating that Rf in *P. notoginseng* plays a neuroprotective role and ameliorates Alzheimer disease—like symptoms by inhibiting caspase-1 expression, suggesting that targeting caspase-1 by Rf and other agents in the neuro-inflammatory responses might be a potential strategy for Alzheimer disease treatment. Liu et al [79] reported the molecular mechanism by which ginsenoside Rd ameliorates colitis in mice. Oral administration of Rd alleviated the symptoms of colitis and reduced proinflammatory cytokine production in mice with dextran sulfate sodium—induced colitis. In addition, Rd suppressed NLRP3 inflammasome activation, leading to a decrease in caspase-1 activation and IL-1β secretion in mice with colitis [79]. These observations were further confirmed *in vitro* that Rd suppressed NLRP3 inflammasome activation, resulting in caspase-1 deactivation in the human monocyte cell line, and THP-1 cells stimulated with LPS [79]. These results suggest that Rd plays an ameliorative role in colitis by inhibiting the activation of NLRP3 inflammasome and the downstream effector, caspase-1, which provides the idea that targeting NLRP3 inflammasome or caspase-1 could be a potential treatment for colitis. Ginsenoside *compound K* (CK) is a metabolite of the PPD-type saponins of *P. ginseng* and has been attracting much interest because of its biological and pharmacological properties. Recently, Song et al [80] reported the effect of CK on caspase-1 during the pathogenesis of diabetic nephropathy, the diabetes-induced inflammatory renal failure in the HFD-induced diabetic mice. CK markedly ameliorated diabetic nephropathy in mice with HFD/streptozotocin-induced diabetic nephropathy and reduced inflammatory responses in their kidneys. In addition, CK significantly downregulated the expression of NLRP3 inflammasome components, such as NLRP3, ASC, and caspase-1, and proinflammatory cytokines, IL-1β and IL-18, in both the mice with disease and rat glomerular mesangial cell line, HBZY-1 cells [80]. Moreover, caspase-1 inhibition by its specific inhibitor, VX-765 confirmed CK-suppressed IL-1β production in HBZY-1 cells [80]. This study provides the evidence that CK plays a protective role in diabetes-induced inflammatory diabetic nephropathy, which is associated with downregulation of NLRP3 inflammasome components, including caspase-1, and also suggests the therapeutic implication for the diabetes-induced inflammatory renal injury. Ginsenoside Rg3 is the main bioactive ginsenoside in *P. ginseng* and has reportedly exerted various pharmacological effects. However, Rg3 has been poorly studied in mast cell—induced allergic inflammation. Kee and Hong [81] investigated the effect of Rg3 on caspase-1 in allergic inflammation by using rat mast cell lines. Rg3 reduced histamine production and release from mast cells, HMC-1 and RBL-2H3, by inhibiting caspase-1 activation and also protected mice against anaphylaxis shock stimulated by IgE and compound 48/80, indicating that Rg3 can be a therapeutic agent that could treat allergic inflammatory diseases. AD2 (20(R)-dammarane-3b, 12b, 20, 25-tetrol; 25-OH-PPD; 25-OCH3-PPD) is a rare ginsenoside, and Su et al [82] evaluated the antihepatic fibrosis effect of AD2 prepared from *P. notoginseng* and its underlying mechanism by using mice with thioacetamide-induced hepatic fibrosis. AD2 exhibited an antihepatic fibrosis effect by inhibiting inflammatory molecules, including caspase-1 associated with the pathogenesis of hepatic fibrosis in the liver tissues of mice with thioacetamide-induced hepatic fibrosis, suggesting that AD2 could be a potential pharmacological agent in ameliorating liver fibrosis by targeting inflammatory caspase-1.

Despite the strong evidence of the ginsenoside-mediated inhibitory effect on caspase-1 in the inflammatory responses and diseases, several studies explored the caspase-1 inhibitory effect of the mixture of ginseng components and other herbal agents. Saengmaeksan (SMS) is a Korean traditional herbal prescription comprising Ginseng Radix, *P. ginseng* root, and two different herbal agents, Liriopis Tuber and Schisandrae Fructus, and has been reported to be commonly used in Korea in treating some diseases, including respiratory and cardiovascular diseases. Jeong et al [83] investigated the caspase-1-tagerted anti-inflammatory effect of SMS in mouse peritoneal macrophages. SMS reduced the inflammatory responses by inhibiting the production of inflammatory mediators, such as cyclooxygenase-2 and nitric oxide, and suppressing the activation of NF-κB and caspase-1 in the mouse

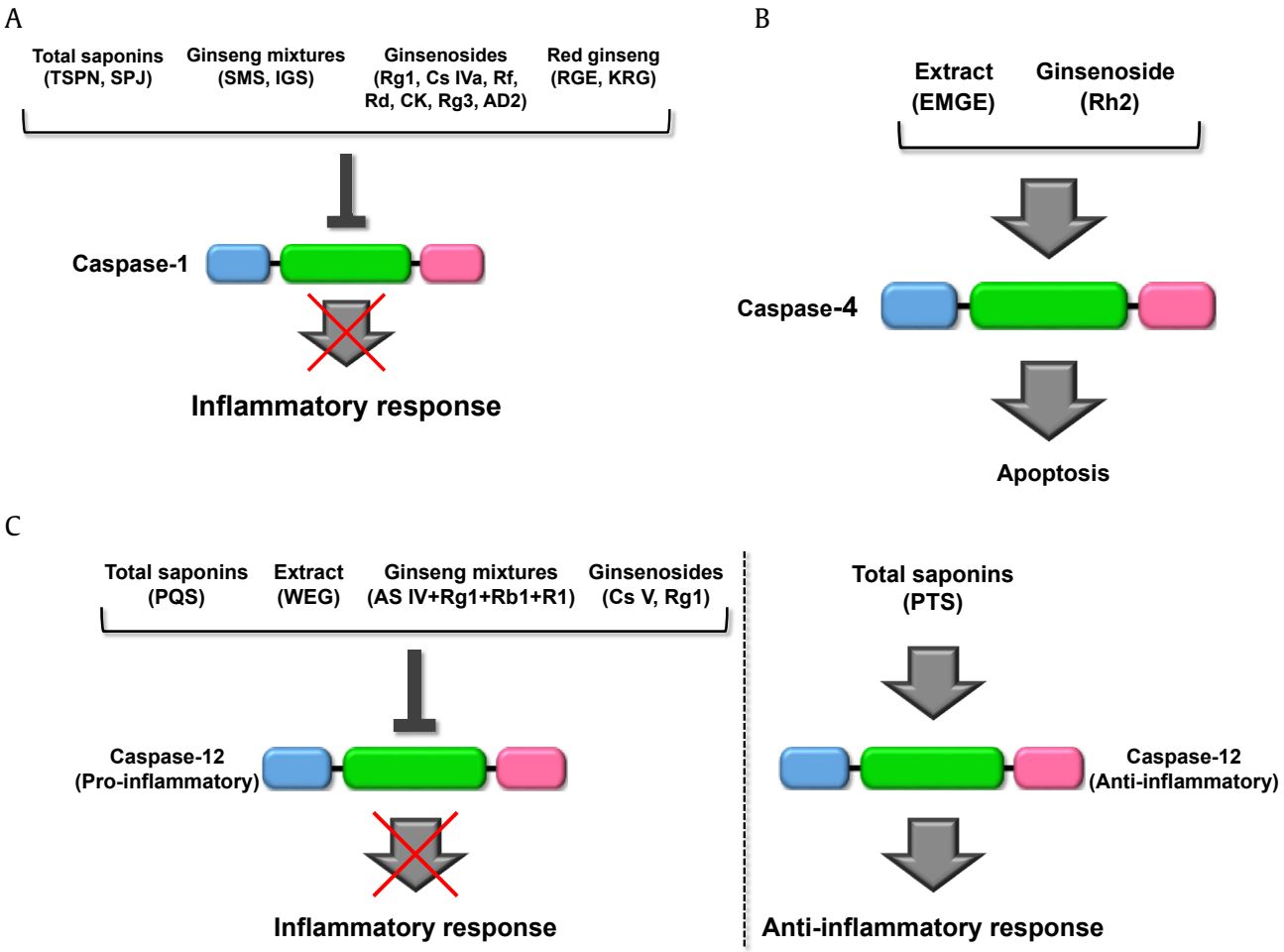

Fig. 3. Regulatory roles of ginseng on inflammatory caspases (A) The indicated ginseng preparations (total saponins, ginseng mixtures, ginsenoside, and red ginseng) suppress caspase-1, and consequently, caspase-1–induced inflammatory responses are inhibited. (B) The ginseng extract (EMGE) and ginsenoside (Rh2) promote the apoptotic function of caspase-4, which induces apoptosis. (C) The indicated ginseng preparations (total saponins, ginseng extract, ginseng mixture, and ginsenosides) suppress caspase-12, which plays a proinflammatory role, and consequently, caspase-12–induced inflammatory responses are inhibited (left). Although ginseng total saponins, PTS, promotes caspase-12, which plays an anti-inflammatory role and induces anti-inflammatory responses. TSPN, total saponins of *Panax notoginseng*; SPJ, total saponins of Japanese ginseng, *Panax japonicas*; SMS, Saengmaeksan; IGS, Igongsan; Cs Via, Chikusetsu saponin Iva; CK, compound K, RGE, Korean Red Ginseng extract; KRG, extract of Korean Red Ginseng; EMGE, enzyme-modified ginseng extract; PQS, total saponins of *Panax quinquefolium*; WEG, water extract of *Panax ginseng*; AS IV, Astragaloside IV; Cs V, Chikusetsu saponin V; PTS, total protopanaxatriol (PPT) saponins of *Panax notoginseng*.

peritoneal macrophages stimulated with LPS, suggesting that SMS can potentially be used as an anti-inflammatory prescription that contains a ginseng component to treat inflammatory diseases. Igongsan (IGS) is another Korean traditional herbal prescription containing a ginseng component consisting of five different herbs, Ginseng Radix, Atractylodis Rhizoma Alba, Poria Sclerotium, Glycyrrhizae Radix et Rhizoma, and Citri Unshius Pericarpium has been used to treat various inflammatory diseases. Kim et al [84] evaluated the caspase-1-targeted anti-inflammatory effect of IGS in the mouse peritoneal macrophages. IGS decreased the production of inflammatory mediators, such as proinflammatory cytokines and prostaglandin E_2 (PGE) and also downregulated the expression of inflammatory genes, such as cyclooxygenase-2 and inducible nitric oxide synthase, in the mouse peritoneal macrophages stimulated with LPS. In addition, IGS inhibited NF-κB and caspase-1 activation in LPS-stimulated mouse peritoneal macrophages [84], strongly suggesting that IGS plays an anti-inflammatory role by negatively modulating inflammatory caspase-1 and NF-κB pathway activation in macrophages. These results provide insights into the development of IGS as a novel anti-inflammatory prescription to treat inflammatory diseases by targeting NF-κB and inflammatory caspase-1.

As discussed earlier, fresh ginseng easily decays because of the high quantity of moisture, and demoisturizing fresh ginseng by repeated steaming and drying produces red ginseng, which has higher contents of bioactive constituents and lowers adverse effects compared with fresh ginseng [30]. Therefore, several studies investigated the regulatory effect of red ginseng on caspase-1 activation in inflammatory responses. Kim et al [85] prepared Korean Red Ginseng (KRG) extract (RGE) and investigated its effect on inflammasome activation in human and mouse macrophages. RGE inhibited both NLRP3 and AIM2 inflammasome activation, resulting in caspase-1 activation, IL-1β secretion, and pyroptosis significantly suppressed in the RGE-treated mouse BMDMs and THP-1 cells. In addition, ginsenosides Rg1 and Rh3 were identified as critical components in RGE to inhibit the activation of these inflammasomes in macrophages [85]. These results suggest that RGE, especially two Rg1 and Rh3 ginsenosides in RGE have an anti-inflammatory activity by inhibiting the activation of NLRP3 and AIM2 inflammasomes and their common downstream effector, caspase-1 in macrophages. Kim et al [86] also prepared the Korean Red Ginseng (KRG) extract and investigated its effect on caspase-1 in the drug-induced adverse effect, irreversible sensorineural hearing damage. KRG protected cisplatin-induced exacerbation of

Table 1
Summary of the studies discussed in the review

Caspase	Type	Compound	Roles	Models	Ref.
Caspase-1	Total saponins	TSPN	• TSPN reduced caspase-1 mRNA expression in cerebral ischemia-reperfusion injury rats	Rats cerebral ischemia-reperfusion injury	[72]
		SPJ	• SPJ improved cognitive decline in aging rats • SPJ reduced caspse-1 expression in aging rats	Aging rats with cognitive decline	[75]
	Ginsenoside	Rg1	• Rg1 reduced symptoms and biomarkers of allergic rhinitis in mice • Rg1 inhibited caspase-1 activation in nasal mucosa tissue of disease mice	Mice with allergic rhinitis	[76]
		Cs IVa	• Cs IVa ameliorated HFD-induced inflammation in adipose tissue of mice • Cs IVa inhibited activation of NLRP3 pathway and caspase in mice and BMDMs	Mice with HFD-induced inflammation	[77]
		Rf	• Rf ameliorated Aβ-induced inflammatory responses by downregulating caspase-1 expression and facilitated Aβ clearance in mutant APP695-transfected N2A cells • Rf administration significantly improved neuronal functions in Aβ-induced Alzheimer disease mice	APP695-transfected N2A cells Mice with Alzheimer disease	[78]
		Rd	• Rd alleviated colitis symptoms and reduced proinflammatory cytokine production in DSS-induced mice with colitis • Rd suppressed the activation of NLRP3 inflammasome and caspase-1 in LPS-stimulated THP-1 cells	LPS-stimulated THP-1 cells Mice with colitis	[79]
		CK	• CK ameliorated diabetic nephropathy symptoms in mice with HFD/STZ-induced diabetic nephropathy and HBZY-1 cells • CK downregulated expression of NLRP3 inflammasome components, including caspase-1 and proinflammatory cytokines • Caspase-1 inhibition suppressed proinflammatory cytokine production	HBZY-1 cells Mice with diabetic nephropathy	[80]
		Rg3	• Rg3 reduced histamine production and release from mast cells by inhibiting caspase-1 activation • Rg3 protected mice against anaphylaxis shock	HMC-1 and RBL-2H3 cells Mice with anaphylactic shock	[81]
		AD2	• AD2 exhibited antihepatic fibrosis effect by inhibiting caspase-1 in the hepatic fibrosis mouse livers	Mice with hepatic fibrosis	[82]
	Ginseng mixture	SMS	• SMS reduced COX-2 and NO production in LPS-stimulated peritoneal macrophages • SMS inhibited caspase-1 and NF-κB in LPS-stimulated peritoneal macrophages	LPS-stimulated mouse peritoneal macrophages	[83]
		IGS	• IGS decreased proinflammatory cytokine and PGE_2 production and downregulated COX-2 and iNOS expression in LPS-stimulated peritoneal macrophages • IGS inhibited caspase-1 and NF-κB in LPS-stimulated peritoneal macrophages	LPS-stimulated mouse peritoneal macrophages	[84]
	Red ginseng	RGE	• RGE suppressed NLRP3 and AIM2 inflammasome activation in BMDMs and THP-1 cells • RGE inhibited caspase-1 activation, IL-1β secretion, and pyroptosis in BMDMs and THP-1 cells • Rg1 and Rh3 of RGE suppressed NLRP3 and AIM2 inflammasome activation in BMDMs and THP-1 cells	BMDMs and THP-1 cells	[85]
		KRG	• KRG protected cisplatin-induced hearing damage of mice • KRG prevented cisplatin-induced cellular cytotoxicity, cytochrome c release, and production of ROS and IL-6 in cisplatin-stimulated HEI-OC1 cells • KRG inhibited NF-κB and caspase-1 activation in cisplatin-stimulated HEI-OC1 cells	Cisplatin-stimulated HEI-OC1 cells Cisplatin-injected mice	[86]

(*continued on next page*)

Table 1 (*continued*)

Caspase	Type	Compound	Roles	Models	Ref.
Caspase-4	Extract	EMGE	• EMGE inhibited proliferation of HepG2 cells • EMGE upregulated mRNA expression of caspase-4 in HepG2 cells	HepG2 cells	[88]
	Ginsenoside	Rh2	• Rh2 inhibited proliferation of H1229 cells • Rh2 upregulated mRNA expression of caspase-4 in H1229 cells	H1229 cells	[91]
Caspase-12	Extract	WEG	• WEG restored PC12 cell viability reduced by corticosterone • WEG attenuated corticosterone-induced apoptosis of PC12 cells • WEG reduced ROS generation and caspase-12 expression in corticosterone-stimulated PC12 cells	Corticosterone-stimulated PC12 cells	[94]
	Ginseng mixture	AS IV Rg1 Rb1 R1	• Ginseng mixture ameliorated cerebral ischemia-reperfusion injury in mice • Ginseng mixture recovered neurocyte survival rate and reduced neurocyte apoptosis • Ginseng mixture suppressed expression of caspase-12 and proinflammatory cytokines, TNF-α, and IL-1β in the brain of the diseased mice	Mice with cerebral ischemia-reperfusion injury	[95]
	Ginsenoside	Cs V	• Cs V protected SH-SY5Y cell death • Cs V reduced ROS generation and caspase-12 expression in MPP^+-stimulated SH-SY5Y cells • Cs V upregulated Sirt1 and Mn-SOD expression in MPP^+-stimulated SH-SY5Y cells	MPP^+-stimulated SH-SY5Y cells	[96]
		Rg1	• Rg1 attenuated progression of HFD-induced fatty liver disease • Rg1 inhibited lipid peroxidation and caspase-12 expression in HFD-induced NAFLD mice • Rg1 suppressed activation of NLRP3 inflammasome and secretion of IL-1β and IL-18 in HFD-induced NAFLD mice	Mice with HFD-induced NAFLD	[98]
	Total saponins	PQS	• PQS protected cardiomyocytes from H/R-induced injury and apoptosis • PQS suppressed ER stress and caspase-12 activation in H/R-injured cardiomyocytes	Rat cardiomyocytes	[93]
		PTS	• PTS ameliorated acetaminophen-induced liver injury in mice • PTS decreased serum levels of ALT and TNF-α in acetaminophen-induced liver injury mice • PTS restored caspase-12 expression decreased by acetaminophen in mouse livers	Mice with liver injury	[100]

AS IV, astragaloside IV; TNF-α, tumor necrosis factor-α; PTS, total protopanaxatriol (PPT) saponins of *Panax notoginseng*; ALT, alanine aminotransferase; PQS, total saponins of *Panax* quinquefolium; HFD, high-fat diet; TSPN, total saponins of *Panax notoginseng*, SPJ, total saponins of Japanese ginseng; Cs IVa Chikusetsu saponin IVa; BMDMs, bone marrow–derived macrophages; RGE, Korean Red Ginseng extract; NLR, nucleotide-binding and oligomerization domain-like receptor; LPS, lipopolysaccharide; DSS, dextran sulfate sodium; CK, compound K; STZ, streptozotocin; SMS, Saengmaeksan; NF-κB, nuclear factor-kappa B; IGS, Igongsan; COX-2, cyclooxygenase-2; PGE_2, Prostaglandin E2; iNOS, inducible nitric oxide synthase; AIM2, absent in melanoma 2; KRG, Korean Red Ginseng; Cs V, Chikusetsu saponin V; EMGE, enzyme-modified ginseng extract; ROS, reactive oxygen species; NAFLD, nonalcoholic fatty liver disease; H/R, hypoxia-reoxygenation; MPP, 1-methyl-4-phenylpyridinium ion; WEG, water extract of *P. ginseng*.

Table 2
Different aspects between apoptosis and pyroptosis

Definition	Apoptosis	Pyroptosis
	Programmed process of autonomous cell death to avoid eliciting inflammation	Novel form of cell death mediated by pathogen infection to elicit inflammation
Molecules involved	• Initiator caspases - Caspase-2/8/9/10 • Effector caspases - Caspase-3/6/7 • Proapoptotic and antiapoptotic Bcl-2 family	• Inflammasomes - NLR family, AIM2, caspase-4/5/11 • Caspase-1 • GSDMD
Features	• Cell blebbing and shrinking • Apoptotic body formation • Condensation and fragmentation of nucleus • Phosphatidylserine exposure	• GSDMD-mediated pore formation • Cell swelling and rupture by osmotic balance • Membrane vesicle formation • Release of inflammatory molecules

NLR, nucleotide-binding and oligomerization domain-like receptor; GSDMD, gasdermin D; AIM2, absent in melanoma 2.

the hearing threshold in mice and also prevented cisplatin-mediated cellular cytotoxicity, cytochrome c release, and production of inflammatory mediators, such as reactive oxygen species (ROS) and IL-6 in HEI-OC1 auditory cells. Moreover, KRG inhibited NF-κB and caspase-1 activation in HEI-OC1 cells [86], suggesting that KRG ameliorates drug-induced hearing damage by suppressing inflammatory responses in the auditory cells through the inhibition of NF-κB and caspase-1, and also providing the potential of KRG as a promising remedy that can treat drug-mediated adverse effects.

Taken together, these studies strongly suggest that various ginseng preparations, including total ginseng saponins, single ginsenoside, herbal prescriptions containing ginseng components, and KRG play an anti-inflammatory role by effectively inhibiting inflammatory caspase-1, a downstream common and critical effector of the inflammasome activation pathway in inflammatory responses and diseases (Fig. 3A). Moreover, selective targeting of caspase-1 using ginseng preparations could be a promising strategy to treat various inflammatory diseases by suppressing inflammasome-activated inflammatory responses.

3.2. Effect on caspase-4

As discussed earlier, studies exploring the role of ginseng on inflammatory caspases have mostly focused on caspase-1 because it was first discovered as an inflammatory caspase. However, some studies also showed the role of ginseng on caspase-4, which is recently discovered as an inflammatory caspase [49].

Chronic inflammation causes tumorigenesis, tumor growth, malignant transformation, invasion, and metastasis, and inflammatory mediators during chronic inflammation exhibit multiple effects in the development of various cancers [87]. A study investigating the antitumor growth effect of ginseng by modulating caspase-4 was reported. Jang et al [88] prepared enzyme-modified ginseng extract (EMGE) by pulverizing ginseng roots and evaluated the effect of EMGE on the proliferation of human hepatocarcinoma cell line, HepG2 cells. EMGE significantly inhibited HepG2 cell proliferation; however, genetic analyses by cDNA microarray and quantitative real-time polymerase chain reaction showed that EMGE upregulated mRNA expression of caspase-4 in HepG2 cells. Because caspase-4 is known as an inflammatory caspase, caspase-4 mRNA expression is expected to be downregulated by EMGE to inhibit HepG2 cell proliferation. However, this result is also feasible because caspase-4 plays a dual role in inducing not only inflammatory responses but also endoplasmic reticulum (ER) stress-induced apoptosis [89,90], suggesting the possibility that the EMGE has an antiproliferative effect on cancer cells by facilitating the apoptotic function of caspase-4. Indeed, the EMGE also upregulated the expression of apoptosis-related genes, such as annexin A2, heat shock 70 kDa protein 9, apoptosis-inducing factor, mitochondrion-associated, 1, ubiquinol-cytochrome c reductase core protein II, and caspase-7 in HepG2 cells [88]. Therefore, these results indicate that EMGE plays an antiproliferative role in cancer cells by increasing the expression of caspase-4 and apoptosis-related enzymes. A similar study investigated the antitumor growth activity of ginseng by regulating caspase-4 in lung cancer cells. Ge et al [91] demonstrated the inhibitory role of ginsenoside Rh2 in the proliferation of lung cancer cell line, H1299 cells. Rh2 inhibited H1299 cell proliferation and upregulated caspase-4 expression in H1299 cells. Similar with the result by Jang et al [88], Rh2 suppresses lung cancer cell proliferation by promoting the apoptotic function of caspase-4, which is supported by the additional results that Rh2 induced H1299 cell apoptosis by upregulating the expression of the apoptosis-related genes, such as activating transcription factor 4 and CCAAT/enhancer-binding protein homologous protein [91]. These results indicate that Rh2 inhibits the proliferation of lung cancer cells in a similar way with EMGE by inducing the apoptotic function of caspase-4. Cell death, including apoptosis, plays a critical role in the regulation of inflammatory responses and may be the final outcome of inflammatory responses, which maintains tissue homeostasis by recognizing and removing invading pathogens and clearing dying cells [92], indicating that cell death and inflammatory responses are tightly linked and functionally interplay. Therefore, ginseng-mediated modulation of apoptosis by regulating caspase-4 expression and functions might have crosstalk with the inflammatory responses, suggesting the necessity for further studies that provide more direct evidence of the ginseng-mediated anti-inflammatory effect by inhibiting inflammatory caspase-4.

Taken together, these two studies clearly demonstrated the antitumor growth effect of ginseng in cancer cells by modulating the expression of caspase-4, which plays as an apoptosis inducer (Fig. 3B). However, more studies investigating the regulatory roles of ginseng on caspase-4 functions as an inflammatory caspase during inflammatory responses and diseases are highly required. In addition, no study has investigated the regulatory roles of ginseng on caspase-11 functions, a mouse counterpart of human caspase-4, in the inflammatory responses to date; therefore, studies in this regard are also needed.

3.3. Effect on caspase-12

Unlike other inflammatory caspases, such as caspase-1, 4, 5, and 11, that induce inflammatory responses, caspase-12 was initially reported as an anti-inflammatory caspase that suppresses inflammatory responses by inhibiting caspase-1 activation and IL-1β secretion [67]. In accordance with this

observation, caspase-12 deficiency resulted in increased bacterial clearance and resistance to septic shock in mice [68]. However, a recent study also reported caspase-12 as a proinflammatory caspase to induce caspase-1 activation and IL-1β and IL-18 secretion in the canonical and noncanonical inflammasome responses [70]. Despite these contradictory observations, the roles of ginseng in the regulation of caspase-12 functions have been investigated.

Several studies have reported caspase-12 as a proinflammatory caspase by demonstrating the suppressive effect of ginseng on caspase-12 in the inflammatory responses. Wang et al [93] prepared total saponins from the stems and leaves of *Panax quinquefolium* (PQS) and investigated its protective effect on myocardial ischemia-reperfusion injury in neonatal rat cardiomyocytes injured by hypoxia–reoxygenation. PQS protected the cardiomyocytes from hypoxia-reoxygenation–induced injury and apoptosis. Moreover, PQS also suppressed ER stress and caspase-12 activation in cardiomyocytes [93], indicating that PQS plays a protective role in myocardial ischemia-reperfusion injury by inhibiting ER stress and caspase-12 activation in cardiomyocytes. Jiang et al [94] also investigated the effect of the water extract of *P. ginseng* (WEG) on corticosterone-induced neurotoxicity and caspase-12 in the neuronal cell line, PC12 cells. WEG restored the PC12 cell viability reduced by corticosterone and attenuated the corticosterone-induced apoptosis of PC12 cells. A study of its mechanism further demonstrated that WEG reduced ROS generation and caspase-12 expression in PC12 cells [94]. Huang et al [95] prepared the ginseng mixture consisting of Astragaloside IV, ginsenoside Rg1, ginsenoside Rb1, and notoginsenoside R1 and investigated its effect on caspase-12 in mice with cerebral ischemia-reperfusion injury. Ginseng mixture ameliorated the cerebral ischemia-reperfusion injury in mice by recovering the neurocyte survival rate and reducing neurocyte apoptosis, and this ameliorative effect was accomplished by suppressing the expression of caspase-12 and proinflammatory cytokines, tumor necrosis factor-α and IL-1β, in the mice with the disease.

Similar with ginseng extract and ginseng mixture, the suppressive effect of single ginsenoside on caspase-12 in the inflammatory response was also shown. Yuan et al [96] prepared Chikusetsu saponin V (Cs V) from the Japanese ginseng, *Panax japonicas* and investigated the neuroprotective effect of Cs V in the human neuroblastoma cell line, SH-SY5Y cells. Cs V protected the SH-SY5Y cells against the 1-methyl-4-phenylpyridinium ion (MPP^+)–induced cytotoxicity, and a study of its mechanism revealed that Cs V-mediated neuroprotective effect was achieved by reducing ROS generation and caspase-12 expression and increasing Sirt1, Mn-SOD, and caspase-12 expression in MPP^+-stimulated SH-SY5Y cells. Mn-SOD is an antioxidant enzyme, and Sirt1 protects the tissue from the oxidative stress by upregulating Mn-SOD expression [97]. Therefore, these results suggest that Cs V exerts neuroprotective activity by reducing oxidative stress and inflammatory responses by suppressing ROS generation and proinflammatory caspase-12 expression and inducing antioxidant enzyme expression in neuronal cells. Another study also reported the role of ginsenoside Rg1 on caspase-12 in nonalcoholic fatty liver disease (NAFLD). Xu et al [98] prepared a NAFLD mouse model by HFD and investigated the protective effect of Rg1 on NAFLD in the mice with the disease. Rg1 significantly attenuated the progression of HFD-induced fatty liver disease by inhibiting lipid peroxidation and caspase-12 expression in mice. Moreover, in accordance with previous observation [85,99], Rg1 suppressed the activation of NLRP3 inflammasome response and secretion of IL-1β and IL-18 in mice [98], suggesting that Rg1 plays a protective role in NAFLD by inhibiting caspase-12, lipid peroxidation, and NLRP3 inflammasome activation.

The studies discussed previously successfully showed that ginseng preparations suppress the inflammatory responses by inhibiting caspase-12, which plays a proinflammatory role. By contrast, an interesting study reported caspase-12 as an anti-inflammatory caspase in the inflammatory responses. Acetaminophen, which is widely used as an antipyretic and analgesic agent, induces hepatic necrosis by promoting cytotoxicity and inflammatory responses in the liver, resulting in acute liver failure. Wang et al prepared total protopanaxatriol saponins of *P. notoginseng* (PTS) and investigated its effect on acetaminophen-induced liver failure and caspase-12 in mice. PTS ameliorated acetaminophen-damaged liver injury in mice by reducing the serum levels of alanine aminotransferases and tumor necrosis factor-α and restored caspase-12 expression decreased by acetaminophen in the mouse livers [100], indicating that PTS ameliorates liver injury by reducing cytotoxicity and inflammatory responses by increasing caspase-12 expression in liver. These results might suggest that caspase-12 is an anti-inflammatory caspase rather than a proinflammatory caspase because caspase-12 expression was upregulated by PTS, resulting in the alleviation of liver injury by decreasing inflammatory responses in the liver.

It is still unclear whether caspase-12 plays an anti-inflammatory or proinflammatory role in inflammatory responses and various inflammation-mediated diseases. In addition, caspase-12 has been reported as a dual player critically involved in inflammatory responses and ER stress–induced apoptosis [89,90]. Therefore, ginseng might exert multiple and complicated effects on caspase-12 functions to regulate various biological processes, including inflammatory responses, apoptosis, and other cellular responses. Therefore, further studies investigating the regulatory roles of ginseng in caspase-12 functions in various biological conditions are highly required. Fig. 3C shows the regulatory roles of ginseng on caspase-12 in the inflammatory responses and apoptosis.

4. Conclusion and perspectives

Inflammation is a defense mechanism that protects the body against various pathogens and dangers. Among the two main steps of inflammatory responses, triggering is the essential step in boosting inflammatory responses by activating inflammasomes in response to specific ligands, and inflammatory caspase activation is one of the hallmarks of inflammasome-activated inflammatory responses. To date, several inflammatory caspases have been discovered, and their roles in the inflammatory responses have been demonstrated. Given the evidence of the inflammatory caspases pivotal players in the inflammatory responses and diseases, many studies have focused on the development of anti-inflammatory therapeutics targeting inflammasome pathways and inflammatory caspases for various diseases. However, one of the major drawbacks of the anti-inflammatory small molecule drugs is their severe cytotoxicity and adverse effects; therefore, complementary and alternative medicines have received much attention to overcome these problems associated with the small molecule drugs. Ginseng has long been traditionally used as an herbal medicine in ameliorating various human diseases, and many efforts have been successfully made on identifying the pharmacological components in ginseng and evaluating the anti-inflammatory activity in inflammatory responses and diseases. Interestingly, recent studies have shown the effect of ginseng on inflammatory caspases. Various preparations of ginseng, such as total saponins, extracts, ginseng-containing prescriptions, and ginsenosides isolated from ginseng show the suppressive effect on caspase-1, a first identified inflammatory caspase, and caspase-4, leading to inflammatory response suppression. Although, whether caspase-12 is a proinflammatory or anti-inflammatory

caspase is still controversial, studies showed that ginseng suppresses or promotes caspase-12 functions in inflammatory responses. In addition, because caspase-12 has dual roles involved in inflammatory responses or ER stress–induced apoptosis [89,90], ginseng regulates inflammatory responses and other biological functions by modulating inflammatory responses or apoptosis mediated by caspase-12.

Despite these successful studies reporting the regulatory roles of ginseng on the inflammatory caspases, and several inflammatory caspases have been identified and investigated, identification of new inflammatory caspases, their roles in the inflammatory responses, and the effect of ginseng on these novel inflammatory caspases need to be further investigated. Studies examining whether caspase-12 is proinflammatory or anti-inflammatory and the effect of ginseng on caspase-12 functions in inflammatory responses are also needed because these are still unclear because of the limited number of studies. Moreover, despite many studies demonstrating that caspase-11 as a noncanonical inflammasome playing a pivotal role in the inflammatory responses, studies exploring the regulatory role of ginseng on caspase-11 in the inflammatory responses are highly required.

In conclusion, this review discussed the roles of ginseng to suppress inflammatory responses by regulating the functions of inflammatory caspases, as summarized in Table 1, and further suggested the insight into the potential of ginseng as a complementary and alternative medicine with strong anti-inflammatory action by modulating the functions of inflammatory caspases. Selective targeting the inflammatory caspases or intervention of functional interplay between inflammasomes and the downstream effectors, inflammatory caspases using ginseng preparations may be a promising approach for the development of efficacious and safe anti-inflammatory therapeutics to prevent and treat various inflammatory and inflammation-related diseases (Table 2).

Conflicts of interest

The authors declare that they have no conflict of interests regarding the contents of this article.

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