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Review Article

Potential benefits of ginseng against COVID-19 by targeting inflammasomes

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the pathogenic virus that causes coronavirus disease 2019 (COVID-19), with major symptoms including hyper-inflammation and cytokine storm, which consequently impairs the respiratory system and multiple organs, or even cause death. SARS-CoV-2 activates inflammasomes and inflammasome-mediated inflammatory signaling pathways, which are key determinants of hyperinflammation and cytokine storm in COVID-19 patients. Additionally, SARS-CoV-2 inhibits inflammasome activation to evade the host's antiviral immunity. Therefore, regulating inflammasome initiation has received increasing attention as a preventive measure in COVID-19 patients. Ginseng and its major active constituents, ginsenosides and saponins, improve the immune system and exert anti-inflammatory effects by targeting inflammasome stimulation. Therefore, this review discussed the potential preventive and therapeutic roles of ginseng in COVID-19 based on its regulatory role in inflammasome initiation and the host's antiviral immunity.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a strain of single-stranded RNA-enveloped coronavirus that belongs to the *genus Betacoronavirus of* the *Coronaviridae* family and causes coronavirus disease 2019 (COVID-19), which is the respiratory disease responsible for the ongoing COVID-19 pandemic [1]. SARS-CoV-2 has had detrimental effects globally, with a large number of casualties and huge economic and social crises. SARS-CoV-2 encodes nucleocapsid, membrane, envelope, and spike proteins [2,3]. It primarily affects the respiratory tract, particularly lungs, and causes various symptoms such as fever, ageusia, anosmia, shortness of breath, cough, and chest pain [4]. Although COVID-19 is a respiratory disease, it increases the risk of other serious diseases and life-threatening situations [5]. Despite the recent rapid development of COVID-19 vaccines and therapeutic drugs, the number of COVID-19 patients is still sharply increasing worldwide; therefore, studies identifying and validating therapeutic targets and developing standard therapeutic agents for this deadly disease are highly needed.

COVID-19 is caused by infection-induced pathological inflammatory responses, resulting in excessive inflammatory cytokine release, known as “cytokine storm” and severe organ injuries [6]. Additionally, COVID-19 is highly associated with various comorbidities, including asthma, chronic obstructive pulmonary disease, cardiovascular diseases, hepatic diseases, diabetes, renal diseases, human immunodeficiency syndrome, and cancers, which are closely related to pathogenic inflammatory responses [5]. Therefore, SARS-CoV-2 infection can amplify pathogenic inflammatory responses by activating inflammatory signaling pathways, which worsen COVID-19 symptoms. Accordingly, the suppression of pathogenic inflammatory responses by targeting critical molecules in inflammatory responses could be a useful strategy to alleviate COVID-19 in patients.

Ginseng is a medicinal plant that has long been cultivated in East Asia and North America and is traditionally used to improve physiological conditions and ameliorate disease [7,8]. Various bioactive components have been identified in ginseng, including ginsenosides, polysaccharides, phytosterols, essential oils, glycosides, ginsenosides, and ginseng saponins, are the major active physiological and pharmacological ingredients [9–11]. Over 150 natural ginsenosides and saponins have been identified and reported to play multiple pharmacological roles in diseases, including inflammatory, autoimmune, cardiovascular, metabolic diseases and cancer [11]. Interestingly, recent studies have demonstrated that

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ginseng, particularly ginsenosides and saponins, plays an anti-inflammatory role by inhibiting the activation of inflammasomes [11,12], intracellular multiprotein complexes that provide molecular platforms to activate inflammatory responses [13,14]. Therefore, this review discussed recent studies that highlight the functional involvement of inflammasomes in SARS-CoV-2 infection as well as the inhibitory role of ginseng in inflammasome activation. This review also provided insights into the potential role of ginseng as a promising traditional medicine for the treatment and prevention of COVID-19 by inhibiting inflammasome stimulation.

2. Inflammasomes

2.1. Classification and structures of inflammasomes

Inflammasomes are intracellular protein complexes composing PRRs and inflammatory molecules and provide platforms for inflammatory responses [13,14]. Inflammasomes are mainly classified into canonical and non-canonical inflammasomes. The canonical inflammasomes that were first identified include nucleotide-binding and oligomerization domain (NOD)-like receptor (NLR) family inflammasomes, such as NLRP1, NLRP3, NLPC4, NLPR6, NLRP9, and NLRP12 inflammasomes, and non-NLR family inflammasomes, such as absent in melanoma 2 (AIM2) and pyrin inflammasomes [13,14]. Recent studies have discovered new types of inflammasomes that are distinguishable from canonical inflammasomes and named them non-canonical inflammasomes [15]. Non-canonical inflammasomes include mouse caspase-11 and human caspase-4 and -5 inflammasomes [16–18].

The NLR family of PRRs has similar structures. NLRP1, which was first identified in the NLR family PRRS, has the most complex structure, composed of an *N*-terminal PYD, a nucleotide-binding and oligomerization domain (NACHT), leucine-rich repeats (LRRs), a functional-to-find domain, and a *C*-terminal caspase recruitment domain (CARD) (Fig. 1A). Interestingly, mouse NLRP1 isoforms do not contain PYD in their human homologs. NLRP3, 6, 9, and 12 have similar structures, with the same domains comprising an *N*-terminal PYD, a NACHT, and *C*-terminal LRRs (Fig. 1A). NLRC4 consists of an *N*-terminal CARD, NACHT, and *C*-terminal LRRs (Fig. 1A). Non-NLR family PRRs have different structures than those of NLR family PRRs. Pyrin consists of an *N*-terminal PYD, a B-box-type zinc finger, a coiled-coil, and *C*-terminal B30.2 (Fig. 1A). AIM2 is the simplest PRR, comprising an *N*-terminal PYD and *C*-terminal hematopoietic interferon-inducible nuclear protein 200 (HIN200) (Fig. 1A). Despite different structures of canonical inflammasome PRRs, noncanonical inflammasome PRRs have the same molecular architecture. Mouse caspase-11 and human caspase-4/5 consist of an *N*-terminal CARD and two catalytic domains: a p20 large domain and a p10 small domain at the *C*-terminus (Fig. 1A).

Canonical inflammasomes are assembled through the interaction of PRRs and pro-caspase-1, with or without the help of a bipartite adaptor, ASC. PRRs with PYD (NLRP1, 3, 6, 9, 12, pyrin, and AIM2) form inflammasomes by interacting with pro-caspase-1 with the help of ASC, contrary to PRRs with an absent PYD (NLRC4) that directly interacts with pro-caspase-1 to form an inflammasome. Non-canonical inflammasomes are assembled differently than canonical inflammasomes. Mouse caspase-11 and human caspase-4/5 form non-canonical inflammasomes via oligomerization through direct CARD-CARD interaction.

2.2. Inflammasome-activated inflammatory responses

Inflammasomes are activated by sensing their specific ligands by PRRs, inducing inflammatory responses via successive proteolytic stimulation cascades of several inflammatory molecules. Activation of inflammasomes induces two main inflammatory responses: pyroptosis and secretion of pro-inflammatory cytokines. Initiation of canonical inflammasomes directly promotes the proteolytic activation of caspase-1, and the activated caspase-1 subsequently induces 1) the proteolytic cleavage of GSDMD, leading to the formation of GSDMD pores in membranes and GSDMD pore-mediated pyroptosis, as well as 2) the proteolytic maturation of

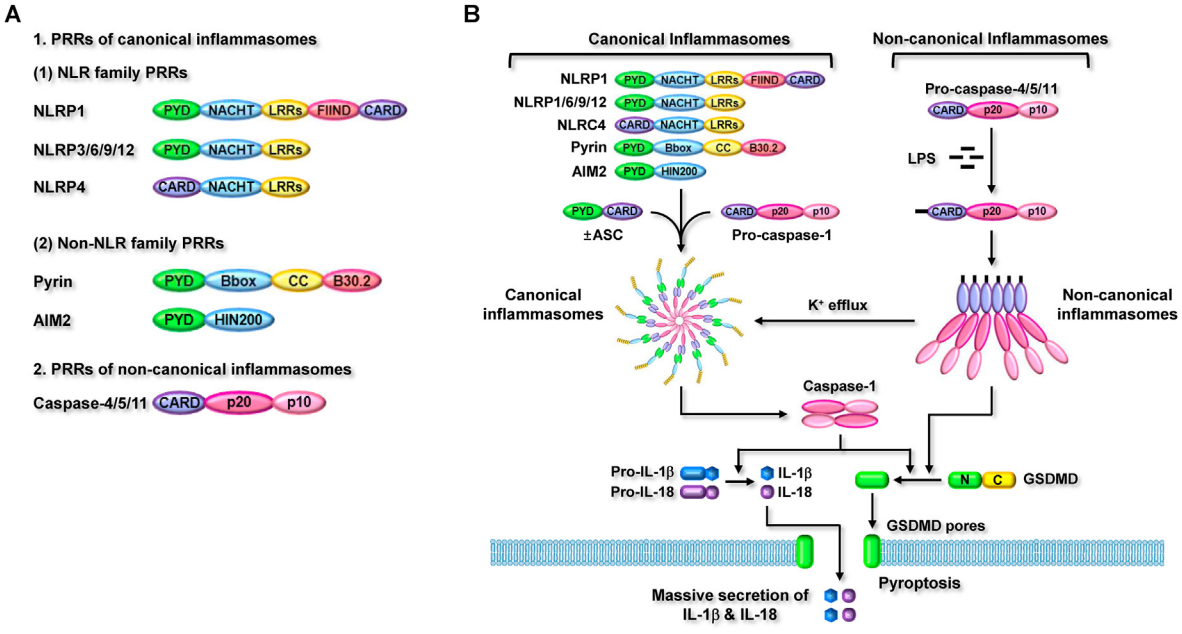

Fig. 1. Inflammasome-activated signaling pathways. Canonical inflammasomes are activated by interaction with pro-caspase-1 with or without the help of ASC, but non-canonical inflammasomes are activated by direct interaction with intracellular LPS. The activated inflammasomes subsequently induce GSDMD proteolysis and GSDMD pore generation, resulting in pyroptosis. The activated inflammasomes also induce proteolytic activation of caspase-1 and caspase-1-mediated maturation of pro-inflammatory cytokines, resulting in the secretion of the pro-inflammatory cytokines through GSDMD pores.

IL-1β and IL-18, leading to secretion through GSDMD pores [13,14]. Non-canonical inflammasome-activated inflammatory responses are similar, but not the same as those mediated by canonical inflammasomes. Stimulation of non-canonical inflammasomes directly induces proteolysis, pore formation, and pore-mediated pyroptosis of GSDMD, but indirectly activates caspase-1 through canonical inflammasome activation [12,19–21]. The stimulation of non-canonical inflammasomes induces canonical inflammasome activation, resulting in caspase-1 activation and caspase-1-mediated maturation and secretion of IL-1β and IL-18 through GSDMD pores [12,19–21].

As discussed above, the stimulation of caspase-1 by non-canonical inflammasomes is promoted by functional cooperation between canonical and non-canonical inflammasomes. Potassium ion (K^+) efflux by membrane damage and membrane gate proteins, such as GSDMD pores, P_2X7 channels, bacterial pore-forming toxins, and pannexin 1 channel, is the main cause of NLRP3 canonical inflammasome activation [13,14]. Recent studies have demonstrated that caspase-11 non-canonical inflammasome activation induces K^+ efflux, resulting in NLRP3 canonical inflammasome activation [22,23]. This strongly suggests that canonical and non-canonical inflammasomes have functional crosstalk rather than independent roles in inducing inflammatory responses. However, the functional relationship between canonical and non-canonical inflammasomes is still poorly understood and needs to be further elucidated. Inflammasome-activated inflammatory responses are summarized in Fig. 1B.

3. Regulatory roles of SARS-CoV-2 infection in inflammasome initiation

3.1. NLRP3 inflammasome

SARS-CoV-2 infection induces hyper-inflammation and a consequent cytokine storm, and many studies have reported that SARS-CoV-2-infected hyper-inflammation and cytokine storm are mediated by stimulation of the NLRP3 inflammasome. In vitro studies have clearly demonstrated that SARS-CoV-2 infection activates the NLRP3 inflammasome in various cell types. SARS-CoV-2 S protein activates the NLRP3 inflammasome in Cacp-2 cells [24], and SARS-CoV-2 viroporin encoded by ORF3a triggers the NLRP3 inflammasome pathway in A549 cells [25]. In vitro studies of SARS-CoV-2-induced NLRP3 inflammasome activation have also been conducted in macrophages, human peripheral blood mononuclear cells (PBMCs), hematopoietic stem/progenitor cells (HSPCs), and endothelial progenitor cells (EPCs). Single-stranded RNA genome sequences of SARS-CoV-2 activate the NLRP3 inflammasome in human macrophages differentiated from PBMCs [26], and SARS-CoV-2 envelope protein also activates the NLRP3 inflammasome in mouse bone marrow-derived macrophages (BMDMs) [27]. SARS-CoV-2 nucleocapsid protein also induces hyper-inflammation by stimulating the NLRP3 inflammasome in mouse BMDMs, human monocytes, and THP-1 cells [28]. Interestingly, SARS-CoV-2 nonstructural proteins NSP1 and NSP13, however, suppress NLRP3 inflammasome activation in monocytes [29]. This indicates that different proteins in the same SARS-CoV-2 can play different roles in NLRP3 inflammasome stimulation during inflammatory response. SARS-CoV-2 replicates via the mechanism that allows for its escape from inflammasome-activated antiviral immunity. The SARS-CoV-2 spike protein induces hyper-inflammation and exaggerated production of pro-inflammatory cytokines by activating the NLRP3 inflammasome in human PBMCs [30]. The SARS-CoV-2 spike protein also damages HSPCs and EPCs by inducing NLRP3 inflammasome activation and subsequent pyroptosis [31]. The SARS-CoV-2 spike protein has been demonstrated in vitro to interact with its molecular receptor, angiotensin-converting enzyme 2 (ACE2) [32,33], leading to the stimulation of the NLRP3 inflammasome in HSPCs and EPCs [34].

The regulatory role of SARS-CoV-2 in NLRP3 inflammasome activation has also been evaluated in various types of cells in COVID-19 patients. The primary site of SARS-CoV-2 infection is the respiratory system; therefore, the modulatory role of SARS-CoV-2 in NLRP3 inflammasome initiation has been reported in lungs and airway of COVID-19 patients. SARS-CoV-2 NSP6 triggers pyroptotic death of lung epithelial cells in COVID-19 patients by activating the NLRP3 inflammasome [35]. In contrast to these results, NLRP3 inflammasome activation was inhibited and NLRP3-activated inflammatory responses were attenuated in the upper airway tissues of COVID-19 patients with further reduced recruitment of inflammatory cells, macrophages, and neutrophils [36], which may suggest that the role of SARS-CoV-2 depends on the location of respiratory tissues, either to induce hyper-inflammation by activating the NLRP3 inflammasome or evading host antiviral immune response by inhibiting NLRP3 inflammasome activation.

The effect of SARS-CoV-2 infection has also been demonstrated in blood cells and circulating monocytes of COVID-19 patients. The NLRP3 inflammasome is triggered in blood cells of COVID-19 patients, leading to elevated levels of proinflammatory cytokines in serum [37]. SARS-CoV-2 also initiates the NLRP3 inflammasome in circulating monocytes of COVID-19 patients, resulting in pyroptotic death of circulating monocytes and secretion of pro-inflammatory cytokines from the cells [38,39]. Interestingly, NLRP3 inflammasome activation in response to SARS-CoV-2 infection is associated with COVID-19 severity [39].

Although the respiratory system is the primary target of SARS-CoV-2 infection, many COVID-19 patients exert mind and severe neurological manifestations [40,41], which indicates the potential for neurotropism and neuropathogenesis by SARS-CoV-2 through inducing neuroinflammation, and some studies reported the regulatory role of SARS-CoV-2 in NLRP3 inflammasome activated neuroinflammation. An in vitro study demonstrated that SARS-CoV-2 spike protein induces neuroinflammation by activating the NLRP3 inflammasome and NLRP3 inflammasome-activated inflammatory signaling pathways in BV2 microglial cells [42]. A case study of deceased COVID-19 patients also reported that SARS-CoV-2 nucleocapsid protein was co-localized with ACE2 and NLRP3 inflammasome in the cerebral cortical tissue-resident macrophages of deceased COVID-19 patients [43], which strongly suggests the involvement of NLRP3 inflammasome in SARS-CoV-2 cerebral pathogenicity.

Age is one of the most critical factors associated with mortality risk due to SARS-CoV-2 infection. This risk rapidly increases for people in their 60s and over 80s with serious illnesses and death [44,45]. A recent study demonstrated that age is an important factor in increasing lethality in COVID-19 patients. The NLRP3 inflammasome is over-activated and the production of pro-inflammatory cytokines is highly increased in aged COVID-19 patients [46]. Studies explained the mechanistic reason why the NLRP3 inflammasome is more activated in elderly people. Aging induces deterioration of mitochondrial performance and is highly associated with the increased production of mitochondrial ROS (mtROS), leading to the accumulation of damaged mitochondria [47]. The mtROS-damaged mitochondria release mtDNA which acts as damage-associated molecular patterns (DAMPs), resulting in the induction of the formation and activation of NRLP3 inflammasome and NLRP3 inflammasome-activated inflammatory responses [48,49]. These studies suggest that NLRP3 inflammasome activation and subsequent inflammatory responses play a pivotal role in the increased mortality of elderly COVID-19 patients infected with SARS-CoV-2.

Taken together, SARS-CoV-2 infection induces hyper-inflammation and consequent cytokine storm via activation of the NLRP3 inflammasome and NLRP3 inflammasome-activated inflammatory responses in COVID-19 patients, and also plays an inhibitory role in NLRP3 inflammasome stimulation to escape from the NLRP3 inflammasome-activated host antiviral immunity.

3.2. Other types of inflammasomes – NLRP1, NLRP12, and AIM2

Although most studies have focused on the NLRP3 inflammasome, other inflammasomes have also been reported to be regulated by SARS-CoV-2. A study analyzing gene expression profiles revealed that NLRP1 expression decreased in SARS-CoV-2-infected human lung epithelial cells [50]. This result is similar to those of other studies investigating the inhibitory role of SARS-CoV-2 in NLRP3 inflammasome activation [29,36], suggesting that SARS-CoV-2 also inhibits NLRP1 inflammasome initiation to escape host antiviral immunity.

Unlike ordinary inflammasomes, the NLRP12 inflammasome negatively regulates the secretion of pro-inflammatory cytokines from pyroptotic cells through GSDMD pores [51], which has been identified as the main cause of the cytokine storm observed in COVID-19 patients [52]. In addition, loss-of-function mutations in NLRP12 are associated with inflammatory responses and autoimmune diseases [53], indicating that NLRP12 inflammasome plays an anti-inflammatory role in inflammatory responses and diseases. Interestingly, an in vitro protease assay identified NLRP12 as a direct substrate of SARS-CoV-2 NSP5, resulting in its proteolysis of NLRP12 and hence indicating its role in hyperinflammation [54]. Cell-based experiments also revealed that NLRP12 levels were reduced in SARS-CoV-2-infected HEK293T-ACE2 cells expressing ACE2 [54], suggesting that SARS-CoV-2 induces hyperinflammation by proteolytic inhibition of the NLRP12 inflammasome, which is a negative regulator of inflammatory responses.

The role of SARS-CoV-2 in AIM2 inflammasome activation has also been previously reported. SARS-CoV-2 activates the AIM2 inflammasome in circulating monocytes of COVID-19 patients, hence inducing pyroptotic death and secreting pro-inflammatory cytokines from monocytes [38]. SARS-CoV-2 infection instigated hyper-inflammation by activating not only NLR family inflammasomes, but also non-NLR family inflammasomes, such as the AIM2 inflammasome, in COVID-19 patients.

Most studies have evaluated the effect of SARS-CoV-2 on NLRP3 inflammasome activation; however, those demonstrating SARS-CoV-2-regulated functions of other types of inflammasomes, particularly non-canonical inflammasomes, are still limited. Conclusively, SARS-CoV-2 modulates the function of all inflammasomes apart from that of NLRP3, resulting in either hyper-inflammation via pyroptosis and pro-inflammatory cytokine secretion or evasion of host immune surveillance for viral replication and survival. The regulatory roles of SARS-CoV-2 infection in inflammasome stimulation are summarized in Table 1.

4. Inhibitory role of ginseng in inflammasome activation

4.1. NLRP3 inflammasome

The NLRP3 inflammasome is the most studied canonical inflammasome that induces inflammatory responses and diseases. Numerous ginsenosides and ginseng saponins have been demonstrated to inhibit NLRP3 inflammasome activation, resulting in the suppression of inflammatory responses and amelioration of disease conditions. Rb1, Rg1, Rg2, Rg3, Rg5, Rd, Re, Rh1, 25-OCH_3-PPD, and compound K (CK) in *Panax ginseng* inhibit NLRP3 inflammasome stimulation, leading to suppressed inflammatory responses and multiple disease conditions, such as obesity, gouty arthritis, atherosclerosis**, non-alcoholic fatty liver disease, liver injury, hyperlipidemia, type I diabetes,** myocardial hypertrophy and dysfunction, cerebral ischemia and reperfusion injury, colitis, hepatic fibrosis, sepsis, neuronal damage, kidney injury, and cognitive deficits [55–73]. Korean Red Ginseng (KRG) extract and KRG saponin fraction in *Panax ginseng* also inhibited inflammatory responses by inhibiting NLRP3 inflammasome activation in macrophages, monocytes, sepsis mice, and aging mice [65,74]. *Chikusetsu saponin IVa,* a major active triterpenoid saponin in *Panax japonicus*, inhibited NLRP3 inflammasome activation, hence ameliorating obesity and neuroinflammation in macrophages, adipocytes, primary neurons, and postoperative cognitive dysfunction rats [75,76]. PF11, pseudoginsenoside, in *Panax quinquefolius* and saponins in *Panax notoginseng* inhibited NLRP3 inflammasome initiation, attenuating age-related neuroinflammation in macrophages and neurons [77,78].

4.2. NLRP1 inflammasome

Although most studies investigating the inhibitory role of ginseng in inflammasome activation have focused on NLRP3 inflammasome, while several others have also demonstrated the inhibitory role of ginseng in NLRP1 inflammasome stimulation. The NLRP1 inflammasome is another canonical inflammasome in the NLR family, and some studies have reported the inhibitory role of ginsenoside Rg1 in NLRP1 inflammasome activation and diseases. Rg1 in *Panax ginseng* showed neuroprotective effects against neuronal injury and degeneration by hindering NLRP1 inflammasome-activated neuroinflammation in neurons [79]. Rg1 in *Panax ginseng* protected against age-related neuronal damage and senescence by suppressing NLRP1 inflammasome-activated oxidative stress and neuroinflammation in neurons [80].

4.3. AIM2 inflammasome

The inhibitory effect of ginseng on the activation and inflammatory responses of AIM2 inflammasome, a non-NLR family inflammasome, was examined. KRG extract inhibits AIM2 inflammasome initiation and AIM2 inflammasome-activated inflammatory responses in macrophages and acute septic shock, increasing the survival rate of sepsis mice [65]. Rh1 and Rg3, as the key ginsenosides in KRG extract, play an inhibitory role in AIM2 inflammasome activation and inflammatory responses in macrophages and acute septic shock [65]. Fructose-arginine, a non-ginsenoside amino-sugar in the KRG extract, also inhibited AIM2 inflammasome stimulation. Fructose-arginine in the KRG non-saponin fraction attenuated AIM2 inflammasome activation and AIM2 inflammasome-activated inflammatory responses in macrophages [81]. Interestingly, Rh1 and Rg3 in the KRG extract inhibited the stimulation of both AIM2 and NLRP3 inflammasomes [65]; however, fructose-arginine in the KRG non-saponin fraction inhibited only AIM2, but not NLRP3 [81], suggesting that fructose-arginine is a more specific inhibitor of AIM2 inflammasome activation.

4.4. Caspase-11 and caspase-4 inflammasomes

Mouse caspase-11 and human caspase-4/5 are non-canonical inflammasomes that are distinct from canonical inflammasomes. These non-canonical inflammasomes were recently discovered, and many studies have successfully demonstrated their roles in inflammatory responses and diseases, particularly in infectious diseases caused by gram-negative bacterial infection [15–18,82]. However, non-canonical inflammasomes have not received much attention in studies investigating the inhibitory role of ginseng in

Table 1
Regulatory roles of SARS-CoV-2 infection in inflammasome activation.

Types	Roles	Activators/inhibitors	Models	Ref.
NLRP3	Activation	SARS-CoV-2 spike protein	Caco-2	[24]
		SARS-CoV-2 viroporin	HEK293 & A549	[25]
		SARS-CoV-2 single-stranded RNA	Macrophages	[26]
		SARS-CoV-2 envelope protein	BMDMs	[27]
		SARS-CoV-2 nucleocapsid protein	BMDMs & THP-1	[28]
		SARS-CoV-2 spike protein	PBMCs	[30]
		SARS-CoV-2 spike protein	HSPCs & EPCs	[31]
		SARS-CoV-2 spike protein	HSPCs & EPCs	[34]
		SARS-CoV-2 NSP6	Lung epithelial cells of COVID-19 patients	[35]
		SARS-CoV-2	Blood cells of COVID-19 patients	[37]
		SARS-CoV-2	Circulating monocytes of COVID-19 patients	[38]
		SARS-CoV-2	Circulating monocytes of COVID-19 patients	[39]
		SARS-CoV-2 spike protein	BV-2	[42]
		SARS-CoV-2	Cerebral cortical tissues of COVID-19 patients	[43]
		SARS-CoV-2	Aged COVID-19 patients	[46]
	Inhibition	SARS-CoV-2 NSP1 and NSP13	HEK293 & THP-1	[29]
		SARS-CoV-2	Upper airway of COVID-19 patients	[36]
NLRP1	Inhibition	SARS-CoV-2	Lung epithelial cells	[50]
NLRP12	Activation	SARS-CoV-2 NSP5	HEK293T-ACE2	[54]
AIM2	Activation	SARS-CoV-2	Circulating monocytes of COVID-19 patients	[38]

inflammasome activation and inflammasome-activated inflammatory diseases. Several natural compounds, such as flavonoids and plant extracts, have been reported to attenuate inflammatory responses and diseases by inhibiting non-canonical inflammasome [83–89]; however, the inhibitory role of ginseng in non-canonical inflammasome activation has been rarely demonstrated. KRG extract hindered caspase-11 non-canonical inflammasome initiation and downstream inflammatory responses in macrophages [90]. KRG extract also increased the survival rate of mice with sepsis induced by lethal doses of lipopolysaccharides by inhibiting caspase-11 non-canonical inflammasome activation [90]. Interestingly, the anti-cancer effect of Rh2 through the inhibition of caspase-4 non-canonical inflammasome stimulation has been demonstrated in lung cancer. Rh2 suppresses the proliferation of human lung cancer cells and reduces tumor growth by promoting the apoptotic death of lung cancer cells. The anti-cancer effect of Rh2 was accomplished by the restriction of caspase-4 non-canonical inflammasome activation in lung cancer cells [91].

Taken together, ginsenosides and saponins play an anti-inflammatory role by inhibiting the initiation of canonical and non-canonical inflammasomes, including NLRP1, NLRP3, AIM2, and caspase-11, in inflammatory responses and disease (Table 2).

Table 2
Inhibitory role of ginseng in inflammasome activation.

Target	Ginseng	Components	Models	Ref.
NLRP3	Panax ginseng	Rb1	3T3-L1, adipose tissue	[55]
			Gouty arthritic rats	[56]
		Rg1	NAFLD mice	[57]
			Liver injury mice	[58,59]
			BNCC337685, diabetic nephropathy rats	[60]
			Diabetic mice	[61]
			Cardiomyocytes, myocardial injury mice	[62]
		Rg2	KC, NAFLD mice	[63]
		Rg3	RAW264.7, sepsis mice	[64]
			BMDMs, THP-1, sepsis mice	[65]
			HK-2, kidney injury mice	[66]
			AC16, HCM, cardiomyocytes, myocardial hypertrophy rats	[67]
		Rg5	Diabetic nephropathy mice	[68]
		Rd	THP-1, colitis mice	[69]
			Cerebral IRI mice	[70]
		Re	Memory impairment mice	[71]
		Rh1	BMDMs, THP-1, sepsis mice	[65]
			KC, NAFLD mice	[63]
		25-OCH_3-PPD	HSC-T6, hepatic fibrosis mice	[72]
		CK	Atherosclerotic mice	[73]
			3T3-L1, adipose tissue	[55]
		KRG extract	BMDMs, THP-1, sepsis mice	[65]
		KRG saponins	Aging mice	[74]
	Panax japonicus	CS IVa	BMDMs, adipocytes, obese mice	[75]
			Neurons, POCD rats	[76]
	Panax quinquefolius	PF11	Cognition impaired mice	[77]

Table 2 (*continued*)

Target	Ginseng	Components	Models	Ref.
	Panax notoginseng	Total saponins	Aging rats	[78]
NLRP1	Panax ginseng	Rg1	Neuronal injury mice	[79]
		Rg1	Hippocampal neurons, neuronal injury mice	[80]
AIM2	Panax ginseng	Rg3	BMDMs, THP-1, sepsis mice	[65]
		Fructose-arginine	BMDMs	[81]
Caspase-11	Panax ginseng	KRG extract	J774A.1, sepsis mice	In press
Caspase-4		Rh2	Human lung cancer cells	[91]

5. Conclusions and perspectives: Therapeutic potential of ginseng in SARS-CoV-2 pathogenesis and COVID-19

After identifying SARS-CoV-2 as a pathogenic virus causing the ongoing global pandemic of COVID-19, a huge effort has been made to understand the SARS-CoV-2-infected COVID-19 pathogenesis and underlying mechanisms in COVID-19 patients. This effort has successfully demonstrated that despite cases of mild asymptomatic COVID-19 caused by SARS-CoV-2, SARS-CoV-2 also strongly activates the immune system of host, leading to hyper-inflammation and cytokine storm that cause severe COVID-19, organ injuries, and even death [6]. One of the most critical hallmarks of inflammatory responses and disease pathogenesis is inflammasome activation, which leads to GSDMD pore-mediated pyroptosis and the secretion of pro-inflammatory cytokines through the GSDMD pores [13,14]. SARS-CoV-2 activates various inflammasomes, resulting in severe COVID-19 in many patients with multiple organ injuries due to pyroptotic cell death and cytokine storms due to the massive secretion of pro-inflammatory cytokines. In contrast to these observations, several studies have documented the hindering role of SARS-CoV-2 in inflammasome activation to escape host antiviral immunity. Restricting inflammasome initiation as well as the improvement of host immunity in COVID-19 patients can provide therapeutic benefits.

Ginseng and its main active physiological and pharmacological constituents, ginsenosides and saponins, have been successfully demonstrated as nutraceuticals that ameliorate multiple inflammatory diseases by attenuating the priming step of inflammatory responses [92,93]. Interestingly, ginsenosides and saponins also inhibit the triggering step via attenuating inflammasome activation [11,12]. This provides strong evidence that regular consumption of ginseng as a supplement may reduce the risk of COVID-19

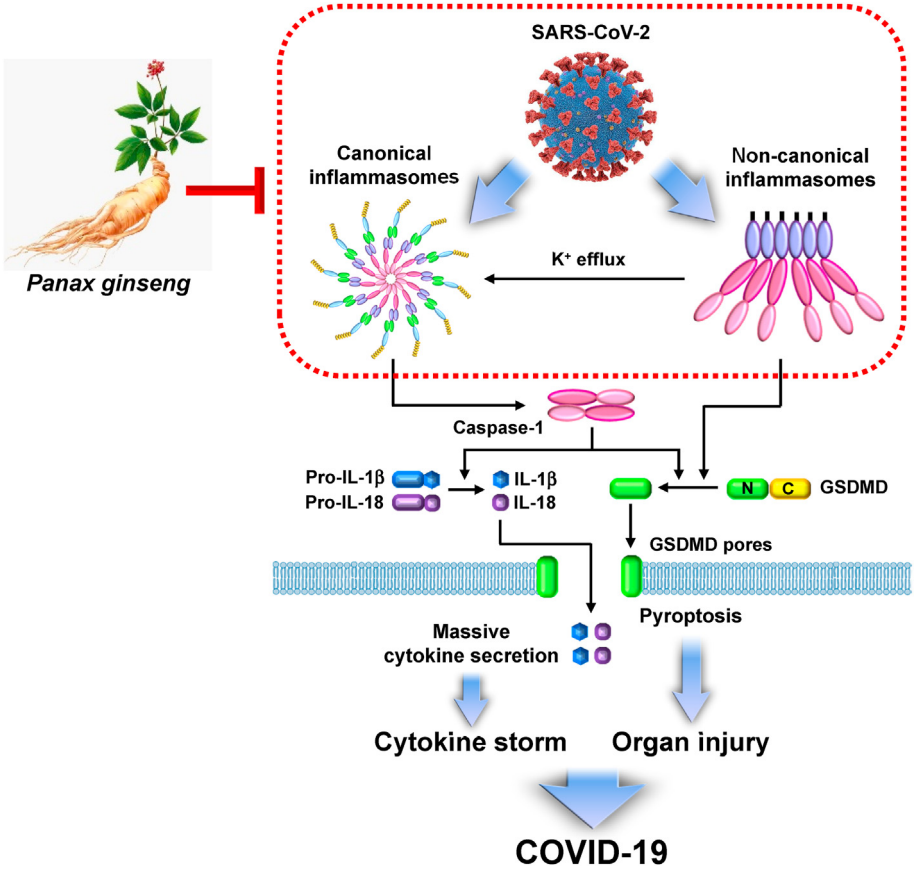

Fig. 2. Graphical summary demonstrating the potential roles of ginseng in SARS-CoV-2-infected COVID-19. SARS-CoV-2 infection induces the activation of canonical and non-canonical inflammasomes, leading to the cytokine storm by massive cytokine secretion and organ injuries by pyroptosis. Ginseng regulates the activation of inflammasomes, which could show potential benefits in COVID-19.

progression, and ginseng and its constituents, ginsenosides, and saponins can be potential herbal medicines to alleviate COVID-19 by inhibiting inflammasome stimulation. Notably, ginseng can ameliorate COVID-19 through a distinct mechanism by inhibiting inflammasome activation and enhancing the host's antiviral immunity [94,95]. The preventive and therapeutic potential of ginseng against COVID-19 via modulation of inflammasome activation is shown in Fig. 2.

Despite these successful studies, direct evidence of ginseng-mediated hindrance of SARS-CoV-2 and alleviation of COVID-19 symptoms have not yet been reported. In addition, the identification and validation of ginsenosides and saponins that can ameliorate COVID-19 by inhibiting inflammasome initiation are in high demand. Moreover, toxicological issues of ginsenosides and saponins need to be evaluated for their effective and safe use in COVID-19 patients.

In conclusion, accumulating evidence strongly suggests that ginseng and its main active ingredients, ginsenosides and saponins, provide preventive and therapeutic benefits by not only inhibiting inflammasome activation and consequent hyper-inflammation, but also promoting the host's antiviral immunity in COVID-19 patients.

Declaration of competing interest

The author declares no conflict of interest.

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