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Review Article

Korean Red Ginseng, a regulator of NLRP3 inflammasome, in the COVID-19 pandemic

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ABSTRACT

Coronavirus disease 2019 (COVID-19) exhibits various symptoms, ranging from asymptomatic to severe pneumonia or death. The major features of patients in severe COVID-19 are the dysregulation of cytokine secretion, pneumonia, and acute lung injury. Consequently, it leads to acute respiratory distress syndrome, disseminated intravascular coagulation, multiple organ failure, and death. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative virus of COVID-19, influences nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain containing 3 (NLRP3), the sensor of inflammasomes, directly or indirectly, culminating in the assembly of NLRP3 inflammasome and activation of inflammatory caspases, which induce the inflammatory disruption in severe COVID-19. Accordingly, the target therapeutics for inflammasome has attracted attention as a treatment for COVID-19. Korean Red Ginseng (KRG) inhibits several inflammatory responses, including the NLRP3 inflammasome signaling. This review discusses the role of KRG in the treatment and prevention of COVID-19 based on its anti-NLRP3 inflammasome efficacy.

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1. Introduction

An atypical viral pneumonia was first reported in December 2019 and spread worldwide as coronavirus disease 2019 (COVID-19) [1]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative virus of COVID-19, is a single-stranded positive-sense RNA virus that belongs to the genus *Betacoronavirus* in the family *Coronaviridae*. SARS-CoV-2 is an enveloped virus consisting of membrane (M), envelope (E), spike (S), and nucleocapsid (N) proteins [2,3]. In addition, it has two viroporins (open reading frame [ORF] 3a and 8a) relating virulence [4]. SARS-CoV-2 primarily infects the respiratory systems and induces fever, sore throat, anosmia, and dyspnea [1,5]. Most COVID-19 infections show mild symptoms, but approximately 10% of the infected people progress to severe pneumonia, some to hypoxia and acute respiratory distress syndrome (ARDS) [1]. In these cases, mechanical ventilation is required, and there is high mortality [1,5]. Severe COVID-19 also presents multiple organ failure and other disorders, such as

acute kidney injury and disseminated intravascular coagulation [6,7]. The symptoms of COVID-19 are mainly respiratory diseases, but cardiovascular and neurological diseases can occur, albeit at a low rate [6,7].

The severity of COVID-19 is caused by an inappropriate hyper-inflammatory response, such as excessive inflammatory cytokine release [6–8]. Furthermore, the infected individual with comorbidities, such as diabetes, heart disease, high blood pressure, and aging, shows a poorer prognosis [7–10]. These comorbidities are tightly related to chronic and persistent activation of nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain containing 3 (NLRP3) inflammasomes [11,12]. Accordingly, hyper-activation of inflammasome signaling will make the symptoms of COVID-19 more severe because it can amplify the inflammatory reaction in people with an excessive inflammatory response [7–10]. The inflammasomes have been considered a causative factor of infectious and metabolic diseases, and the research on inflammasome selective inhibiting drugs is being conducted progressively [11–14]. In particular, studies on discovering anti-inflammasome-modulating substances in food materials are also active [15–25].

Korean Red Ginseng (*Panax ginseng* Meyer), which is prepared by steaming and drying ginseng, is a well-defined medicinal herb

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[26]. Korean red ginseng (KRG) exhibits various pharmacological values, and the properties of inflammation regulation have been well defined [27]. Thus far, many papers have reported the anti-inflammatory effects of KRG and its driven ginsenoside, a unique saponin isolated from ginseng [27,28]. Briefly, ginsenosides attenuated the expression of inflammation-inducing enzymes, such as cyclooxygenases and inducible nitric oxide synthases [27]. Furthermore, inflammatory signals (e.g., prostaglandins and nitric oxides) and cytokines (e.g., interleukin [IL]-1 β , IL-6, and tumor necrosis factor [TNF] α) are also targeted for ginsenosides [27]. Interestingly, KRG and ginsenosides regulate NLRP3 inflammasome activation [23,28]. This review describes the involvement of NLRP3 inflammasome in the pathogenesis of COVID-19. It also discusses the possible role of KRG on COVID-19 treatment and prevention by modulating NLRP3 inflammasome.

2. Inflammasomes

Inflammasomes (Fig. 1), intracellular multi-protein complexes, mediate an inflammation response in the innate immunity and are observed mainly in monocytes, macrophages, and barrier epithelial cells [11,29,30]. The assembly of inflammasomes is triggered by endogenous and exogenous danger signals, such as pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), leading to proinflammatory cytokines (i.e., IL-1 β and IL-18) secretion and inflammatory cell death (i.e., pyroptosis) [11,30]. Several inflammasomes are distinguished by the sensor proteins, such as NLRP3 [11,30]. A priming step precedes the sufficient activation of NLRP3 inflammasome [11,30]. During priming, cells prepare the assembly of NLRP3 inflammasome by upregulating the inflammasome components, such as NLRP3 and precursor of IL-1 β (pro-IL-1 β) via toll-like receptor

(TLR)-nuclear factor (NF)- κ B signal pathways [11,30]. Subsequently, NLRP3 engaged with cytosolic PAMPs or DAMPs recruits an adaptor protein (apoptosis-associated speck-like protein containing a caspase recruitment domain [ASC]) and an effector protein (caspase-1) to form the inflammasomes [11,28,30]. In general, the activation of NLRP3 inflammasome is triggered by the intracellular K⁺ efflux, increase in cytosolic Ca²⁺, and mitochondrial reactive oxygen species (ROS) production [11,31]. In addition, NLRP3 triggers (e.g., adenosine triphosphates [ATP], a bacterial ionophore [nigericin], and crystals of monosodium urates or cholesterols) induce the assembly of NLRP3 inflammasome [11,32–34]. As a non-canonical inflammasome, mouse caspase-11 (caspase-4/5 in humans) interacts with cytoplasmic lipopolysaccharides (LPS) or oxidized phospholipids, leading the cytokine secretion and pyroptosis [35]. The activated caspase-1 and -11 resulting from inflammasome assembly mature IL-1 β and IL-18, and cleavage gasdermin D (GSDMD), a pyroptotic executor [35]. Cleaved GSDMDs oligomerize and form a pore on the cytoplasmic membrane and cellular organelles (e.g., endoplasmic reticulum [ER] and Golgi apparatus) [35,36]. During pyroptosis, the GSDMD pores help drain the cytokines and the alarmins (e.g., ATP, lactate dehydrogenase [LDH], and high mobility group protein B1 [HMGB1]) [37].

3. NLRP3 inflammasome in COVID-19

Monocytes in severe COVID-19 patients display the following evidence of inflammasome activation: a speck formation, which is formed by the aggregation of NLRP3, ASC, and caspase in the cytoplasm; GSDMD pores on the cytoplasmic membrane; pyroptotic cellular morphology [6,38]. In addition, cleaved GSDMD has been detected in the lung tissue and bronchoalveolar lavage fluid (BALF) of severe COVID-19 patients [38]. The serum LDH

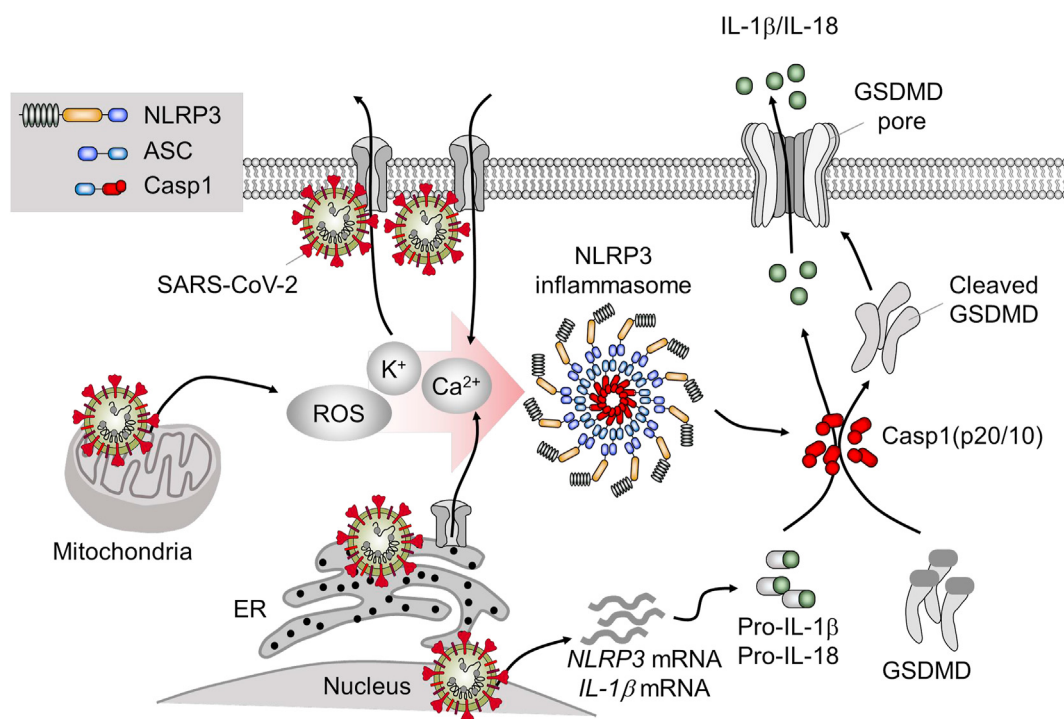


Fig. 1. Molecular mechanisms of NLRP3 inflammasome activation by SARS-CoV-2 infection. SARS-CoV-2 enters the macrophages and monocytes, and activates NLRP3 inflammasome through K⁺ efflux, cytosolic Ca²⁺ influx, and mitochondrial ROS production. Viral E protein stimulates K⁺ efflux and cytosolic Ca²⁺ influx. ORF3a increases K⁺ efflux and mitochondrial ROS production. ORF3a also interacts with ASC leading to assembly NLRP3 inflammasome. The viral S protein disrupts the mitochondrial integrity, resulting in ROS generation, and binds with the NLRP3 protein leading to inflammasome assembly. E protein and ORF3a upregulate the NLRP3 and IL-1 β transcripts through NF- κ B signaling. KRG and ginsenosides attenuate the activation of caspase-1 (Casp1) and the formation of ASC pyroptosome through the inhibition of NLRP3 inflammasome assembly.

concentration increases in severe COVID-19 and is significantly related to the severity of symptoms [39]. LDH is a marker of cell and tissue damage and an indicator of inflammasome-driven pyroptosis [36,37]. Accordingly, this evidence supports the activation of NLRP3 inflammasome in severe COVID-19 [6,39].

As an initial report of a cohort study at the Seafood Market in Wuhan Huanan, the epicenter of COVID-19 increased IL-1 β and IL-1 receptor antagonist (RA) in the patients were observed compared with normal individuals [1]. The levels of IL-1 β were elevated in the BALF and lung tissue of severe COVID-19 patients [40]. The human monocytes infected with SARS-CoV-2 release proinflammatory cytokines, such as IL-1 β , IL-6, and TNF α , which were attenuated by blocking the IL-1 receptor [41]. This suggests that IL-1 β is a trigger of the cytokine release by COVID-19 patients. Furthermore, IL-1 β helps recruit inflammatory cells and secrete proinflammatory cytokines in the lungs, accelerating lung injury by a positive feedback loop [6,38].

Cytokine release syndrome caused by an infection or other stimuli induces fever, hypotension, and hypoxia in response to systemic inflammation [42]. Although most cases of cytokine release syndrome present mild symptoms and recover soon, extraordinary robust cytokine secretion called the cytokine storm leads to high fever, vasodilatory shock, and severe hypoxemia [42,43]. Severe COVID-19 patients display this cytokine storm, rapidly increasing the serum IL-1 β , IL-6, IL-8, IL-10, IL-1RA, and TNF α levels [44]. Hence, inflammasome activation is considered the crux of severe COVID-19 [9]. Data from bats, which are asymptomatic with highly pathogenic coronaviruses, support this [45]. Bat NLRP3 does not respond to coronaviruses, but the bat immune cells expressing human NLRP3 secrete IL-1 β [45].

4. SARS-CoV-2 in NLRP3 inflammasome activation

Highly pathogenic coronaviruses (e.g., SARS-CoV, and Middle East respiratory syndrome coronavirus) trigger NLRP3 inflammasome activation [43]. In addition, SARS-CoV-2 activates NLRP3 inflammasome directly and indirectly through the intracellular signal pathways (Fig. 1).

Based on previous studies, SARS-CoV expresses viroporins (i.e., E protein, ORF3a, and ORF8a), acting as an ionophore. K⁺ efflux and cytosolic Ca²⁺ influx are the common triggers of NLRP3 inflammasome, as mentioned above [6,46]. The E protein of SARS-CoV is related to its virulence, and the mutated E protein reduces the severity in a mouse model [47]. The E protein forms a pore on the plasma membrane and the endoplasmic reticulum-Golgi apparatus intermediate compartment (ERGIC) and elicits K⁺ efflux and cytosolic Ca²⁺ influx leading to NLRP3 inflammasome activation [48]. Furthermore, E protein activates the NF- κ B signaling upregulating proinflammatory cytokines and stimulates the priming step of NLRP3 inflammasome [47]. The ORF3a of SARS-CoV, a pore-forming protein, induces K⁺ efflux and ROS production by disrupting the mitochondria integrity [49]. Furthermore, ORF3a directly activates NLRP3 inflammasome via caspase-1 activation, interaction with ASC, and induction of pyroptosis. ORF3a also upregulates the IL-1 β transcripts [49]. The overexpression of ORF3a of SARS-CoV-2 in A549 cells induced K⁺ efflux and IL-1 β secretion [6]. Consequently, ORF3a and E protein activate NLRP3 inflammasome. When SARS-CoV penetrates the host cells, their S protein interacts with the angiotensin-converting enzyme (ACE) 2 receptor, which degrades angiotensin II [50]. The increased interaction of the S protein and ACE2 receptor elicits the accumulation of angiotensin II [51]. In renal podocytes, angiotensin II induces NLRP3 inflammasome activation via mitochondria dysfunction [52]. The N protein of SARS-CoV activates the complementary cascades, resulting in ATP secretion, cytosolic Ca²⁺ influx, and mitochondria disruption [46].

The N protein of SARS-CoV-2 in macrophages and dendritic cells interacts directly with the NLRP3 protein, leading to the inflammasome assembly and IL-1 β releases [53]. In addition, N protein upregulates the dsRNA-dependent protein kinase through the complementary system and activates NLRP3 inflammasome [54].

5. NLRP3 inflammasome targeting therapy for COVID-19

Targeting cytokine signaling is an appropriate treatment modality for COVID-19 because the cytokine storm in COVID-19 patients aggravates the prognosis [46]. IL-1 receptor antagonists (i.e., anakinra and canakinumab) have been effective in clinical trials and are being used as treatment options [6,46]. On the other hand, there is a clinical trial showing that IL-1 receptor antagonists did not have a therapeutic effect on COVID-19 [55]. This conflicting observation suggests that NLRP3 inflammasome signaling other than cytokines could affect the COVID-19 pathogenesis. The pyroptosis resulting from inflammasome activation is another therapeutic target for COVID-19 pathogenesis [56].

Thus far, several molecules that regulate NLRP3 inflammasome activation have been discovered and applied for therapeutic and research purposes [13]. These inflammasome modulators can also be used in therapeutic trials for COVID-19 [6]. The NLRP3 inflammasome inhibitors (i.e., MCC950 and glyburide) decreased the activity of caspase-1 and the secretion of IL-1 β and IL-6 in human monocytes infected with SARS-CoV-2 [39,41]. Colchicine, which disrupts inflammasome activation by preventing microtubule assembly, decreased the rate of hospitalization and death in COVID-19 patients [57].

Metformin, an anti-diabetes medicine, inhibits NLRP3 inflammasome activation indirectly by interrupting the mechanistic target of rapamycin (mTOR) signaling [58]. Metformin decreased mortality in patients with type 2 diabetes [58]. Furthermore, metformin ameliorated lung inflammation in mice infected with SARS-CoV-2 by inhibiting NLRP3 inflammasome [58]. Disulfiram, a drug for alcohol dependence, and dimethyl fumarate, a medicine for multiple sclerosis, have been shown to block the cleavage of GSDMD followed by the inflammasome activation [59,60]. Interestingly, patients taking disulfiram showed a significantly reduced risk of COVID-19 and no death compared to a control [59]. In addition, patients with multiple sclerosis tended to heal naturally from SARS-CoV-2 infections by being treated with dimethyl fumarate [60]. Thus far, clinical trials are underway to treat severe COVID-19 patients with drugs that inhibit NLRP3 inflammasome activation [46].

6. KRG and ginsenosides on NLRP3 inflammasome activation

The effect of KRG and ginsenosides on inflammasome activation was first discovered in 2014 [23]. In this report, human monocyte-like cells line (i.e., THP-1) and mouse bone marrow-derived macrophages (BMDMs) were exposed to NLRP3 triggers, such as ATP and nigericin, and treated with KRG [23]. KRG dose-dependently inhibited the secretion of IL-1 β and caspase-1 (p20) and the formation of ASC pyroptosome resulting from NLRP3 inflammasome activation [23]. In addition, KRG reduced the lethality of LPS-driven endotoxemia in mice [23]. Ginsenoside Rh1 and Rg3 are considered candidates for inhibiting inflammasome activation, and these two ginsenosides attenuated IL-1 β secretion induced by a NLRP3 trigger [23]. Accordingly, KRG and its ginsenosides have been identified as candidates that inhibit NLRP3 inflammasome activation (Fig. 2). The role of KRG on inflammasome activation was studied in more detail [18]. KRG was divided into a saponin fraction (rich in ginsenosides) and a non-saponin fraction (higher in acidic saccharide content) that were treated in the priming and activation step of

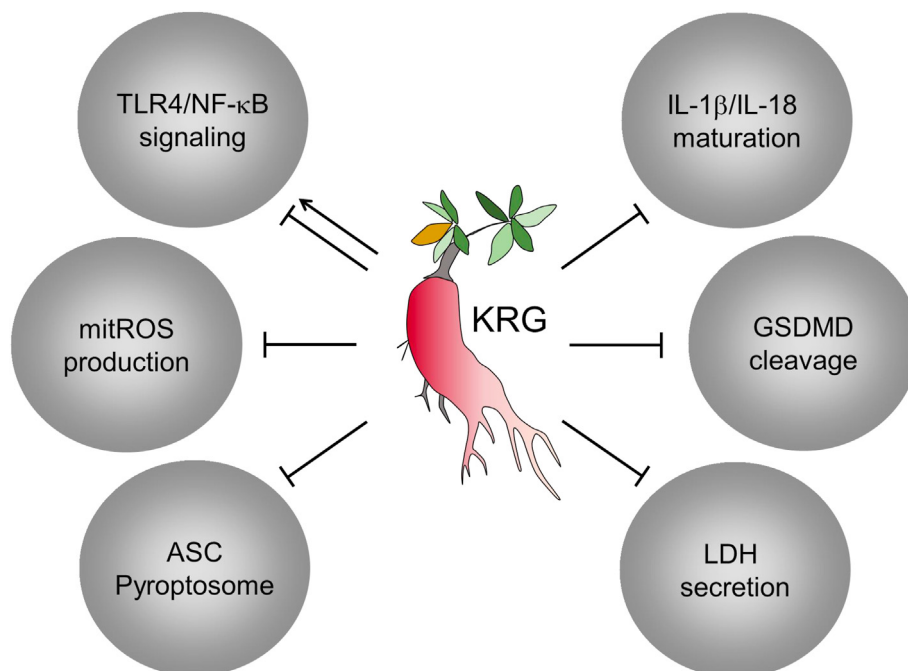


Fig. 2. Role of KRG on NLRP3 inflammasome activation in macrophages and monocytes. Saponins of KRG inhibit TLR4/NF- κ B signaling leading attenuation of inflammatory cytokines and enzymes. On the other hand, non-saponin components of KRG upregulate cytokines and induce the priming step of the inflammasome activation through stimulation of TLR4/NF- κ B signals. KRG attenuates the production of mitochondrial ROS (mitROS) followed by rotenone, a chemical to disrupt mitochondrial integrity (unpublished data). KRG interrupts the formation of ASC pyroptosome, a part of the inflammasome assembly. As KRG inhibits NLRP3 inflammasome activation, it is decreased the maturation of IL-1 β and IL-18, the cleavage of GSDMD, and the secretion of LDH. Accordingly, the excessive inflammatory responses because the positive feedback loops are alleviated.

NLRP3 inflammasome activation in macrophages [18]. During the priming step, the saponin fraction blocked the up-regulation of NLRP3 and pro-IL-1 β transcription and translation [18]. On the other hand, the non-saponin fraction induced gene expression as sufficient for NLRP3 inflammasome activation through the TLR4/NF- κ signaling pathway [18]. At the activation step, the saponin fraction attenuated the secretion of IL-1 β and caspase-1 (p20), and the formation of ASC pyroptosome, while the non-saponin fraction did not affect NLRP3 inflammasome activation [18]. Therefore, the ginsenosides of KRG inhibit both the priming and activation of NLRP3 inflammasome activation [28].

The anti-NLRP3 value of ginsenosides, ginseng, and KRG has been confirmed. Ginsenoside Rg3 inhibited NLRP3 inflammasome activation by disrupting S-nitrosylation in RAW264.7 cells [61]. In addition, Rg3 improved LPS endotoxic septic shock in mice. Compound K, a metabolite of ginseng, reduced the IL-1 β secretion and blocked NLRP3 inflammasome activation [62]. The treatment of compound K alleviates arteriosclerosis in mice, one of the NLRP3 inflammasome-driven diseases. Ginsenoside Rd inhibited the secretion of caspase-1 and IL-1 β , and reduced the severity of dextran sodium sulfate (DSS)-induced colitis, a disease model causing NLRP3 inflammasome activation [63]. Ginsenoside Rg1 attenuated the IL-1 β and IL-18 production in mice with non-alcoholic fatty liver by inhibiting NLRP3 inflammasome [64]. A newly defined ginsenoside, 25-OCH3-PPD, inhibited NLRP3 inflammasome by blocking the P2X7 receptor [65]. Chikusetsusaponin Iva (CS IVa) from *Panax japonicus* decreased the activation of NLRP3 inflammasome, and pyroptosis in the macrophages derived from high fat dieted mice [66]. CS IVa attenuated NLRP3 inflammasome activation in the neurons of postoperative cognitive dysfunction (POCD) rats [67]. Pseudoginsenoside-F11, a saponin derived from *Panax quinquefolius*, blocked the activation of NLRP3 inflammasome, and it ameliorated the neuroinflammation in D-galactose-treated mice [68]. Recently, it was reported that KRG

inhibits the secretion of LDH and the cleavage of GSDMD and caspase-11 resulting from non-canonical inflammasome activation [69]. Based on emerging data, KRG and ginsenosides may be therapeutic candidates for NLRP3 inflammasome-derive disorders, including COVID-19.

7. Discussion

The administration of anti-NLRP3 agents is an important issue in the therapeutic targeting of inflammasome signaling to cure infectious diseases, such as COVID-19 [6]. At the early stages of the inflammation responses to an infection, inflammation, including the NLRP3 inflammasome, is critical for the host defense because it stimulates the recruitment, proliferation, and differentiation of immune cells [70]. Pathogens might spread out if early inflammation is interrupted [70]. Consequently, the beginning of dyspnea, a signal of severe COVID-19 progression, is believed to be the right time for treatment [6]. During dyspnea, anti-NLRP3 inflammasome agents can suppress the cytokine storm and lung injury by blocking the positive feedback loop [6].

Based on previous reports, KRG has been shown to have an inhibitory effect on NLRP3 inflammasome and an improvement effect on various NLRP3 inflammasome-mediated diseases [12,16,23,27,28]. Accordingly, KRG and its active ingredients (e.g., ginsenosides) would prevent or suppress the worsening prognosis of patients with COVID-19. On the other hand, a therapeutic effect of relying solely on KRG would not be expected for severe COVID-19 patients considering the concentration at which KRG would be effective, and it is a complex that modulates various immune responses. Unlike KRG, ginsenoside can be suggested as a therapeutic agent because it is a single molecule that exhibits anti-NLRP3 inflammasome signaling at relatively low concentrations. On the other hand, additional studies, such as toxicological issues, will be

needed before ginsenosides can be proposed as a therapeutic option for COVID-19 patients.

Because KRG has been used as an oriental medicine in Northeast Asia, including Korea, for millennia, there are few safety issues when taken as a nutraceutical [71]. As mentioned above, a SARS-CoV-2 infection has a fatal prognosis in patients with chronic and persistent hyper-activation of NLRP3 inflammasomes, a causative factor for metabolic and degenerative disorders, such as diabetes, hypertension, and aging [6,12,43,46,57]. Therefore, if a patient regularly consumes KRG as a supplement suppressing the hyper-activation of NLRP3 inflammasome might alleviate the progression to severe COVID-19 symptoms. Of note, KRG oppositely regulates the priming and activation steps of NLRP3 inflammasome depending on its components [18]. That is, the non-saponin fraction of KRG stimulates TLR4/NF- κ signaling and induces the expression of inflammatory cytokines and the inflammasome components (e.g., NLRP3 and pro-IL-1 β), the priming step in preparation to fight pathogens [18]. On the other hand, the saponin fraction inhibits priming and blocks the activation step of NLRP3 inflammasome [18]. Accordingly, the saponin fraction interrupts the secretion of the matured cytokines and various alarmins, and suppresses the pyroptosis leading to stop the cytokine storm and consequent lung injury. Regarding the conflicting characteristics of KRG on NLRP3 inflammasome signaling [18], KRG would be an appropriate supplement to increase the immune capacity or fitness because it prepares the host for the initial inflammation in response to a virus invasion, while it blocks the final execution of NLRP3 inflammasome activation. Therefore, the consumption of anti-NLRP3 nutraceuticals, such as KRG, during the COVID-19 pandemic is expected to reduce NLRP3 inflammasome activation, preventing severe prognoses due to excessive inflammation.

Declaration of competing interest

The author declares no conflicts of interest.

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