Review Article

Panax ginseng as a potential therapeutic for neurological disorders associated with COVID-19; Toward targeting inflammasome

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A B S T R A C T

Coronavirus disease 2019 (COVID-19) is a highly infectious respiratory disease caused by a severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). SARS-CoV-2 infection may cause clinical manifestations of multiple organ damage, including various neurological syndromes. There are currently two oral antiviral drugs—Paxlovid and molnupiravir—that are recognized to treat COVID-19, but there are still no drugs that can specifically fight the challenges of SARS-CoV-2 variants. Nucleotide-binding oligomerization domain-like receptor pyrin domain-containing-3 (NLRP3) inflammasome is a multimolecular complex that can sense heterogeneous pathogen-associated molecular patterns associated with neurological disorders. The NLRP3 activation stimulates the production of caspase-1-mediated interleukin (IL)-1β, IL-18, and other cytokines in immune cells. *Panax (P.) ginseng* is a medicinal plant that has traditionally been widely used to boost immunity and treat various pathological conditions in the nervous system due to its safety and anti-inflammatory/oxidant/viral activities. Several recent reports have indicated that *P. ginseng* and its active ingredients may regulate NLRP3 inflammasome activation in the nervous system. Therefore, this review article discusses the current knowledge regarding the pathogenesis of neurological disorders related to COVID-19 and NLRP3 inflammasome activation and the possibility of using *P. ginseng* in a strategy targeting this pathway to treat neurological disorders.

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1. Introduction

The coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, rapidly became a worldwide public health emergency [1–3]. Although SARS-CoV-2 was initially identified as a respiratory virus, it may affect the entire body. While respiratory complications have been considered to be the major risks for COVID-19 patients, neurological complications have also been shown to increase the lethality [3,4]. Neurological damage in COVID-19 patients is triggered by the inflammatory response of cytokines (e.g., IL-6, IL-12, and TNF-α) after the virus binds to angiotensin-converting enzyme 2 (ACE2) receptor and proliferates in the central nervous system (CNS) [4]. Neurological manifestations can be categorized into

those in the CNS (vertigo, headache, stroke, anosmia, ataxia, seizure, etc.), peripheral nervous system (PNS) (taste/smell/vision impairment and neuropathic pain), and musculoskeletal system [4].

Inflammasomes, a group of subcellular multiprotein complexes, are innate immune system receptors and sensors that control the upregulation of caspase-1 and stimulate inflammation against infectious microbes called pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) and molecules derived from host proteins [5]. Among the different inflammasomes that have been identified to date, the nucleotide-binding oligomerization domain-, leucine-rich repeat- and pyrin domain-containing 3 (NLRP3) inflammasome is particularly pivotal for host immune defenses against various infectious agents [6,7], abundantly expressed in the CNS, and may serve to detect noxious agents or irregularities in the cellular microenvironment [8,9]. Abnormal activation of the NLRP3 inflammasome has also been linked with several neurological disorders [8–10]. Further, NLRP3 inflammasome intensely induces cytokine production as an inflammatory response to SARS-CoV-2 infection [11]. Thus, the NLRP3

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inflammasome may be a potential target for the treatment of neurological disorders associated with COVID-19.

Herbal medicine or phytomedicine can be used as potential cures for viral infections like SARS and middle east respiratory syndrome (MERS) [12—16]. Herbal medicines have been shown to have excellent preventive and therapeutic effects with various mode of actions in clinical and preclinical studies [12—16]. Abundant clinical studies have shown that herbal medicines have promising potential to enhance the immune system and overall patient health while reducing COVID-19 and SARS symptoms [16,17]. *Panax (P.) ginseng*, called "the king of all herbs", plays a importalt role in pharmacopeia, and it is valued for its therapeutic features. *P. ginseng* and its ingredients have various beneficial mechanisms including neuroprotective, anti-oxidative, anti-inflammatory, and anti-viral properties [18]. Recent reports have suggested that *P. ginseng* may improve health status by regulating inflammasome activity in various pathological environments such as viral infection and neurological dysfunction [19—23].

Therefore, in this review, we describe neurological disorders associated with COVID-19 and NLRP3 inflammasome as well as the role of *P. ginseng* in potential therapeutics for the neurological disorders caused by COVID-19 via targeting the NLRP3 inflammasome. An ideal medication for COVID-19 will have immunity enhancing, tissue protection/repair, and antiviral activities.

2. Neurological disorders associated with COVID-19

2.1. Emergence of COVID-19

On March 11, 2020, the World Health Organization (WHO) declared the novel COVID-19 outbreak a global pandemic [24]. According to Our World in Data, as of April 24, 2022 there were 509.66 million total confirmed cases and 6.22 million total confirmed deaths because of COVID-19 worldwide (https://ourworldindata.org/about). There have been various mutations in SARS-CoV-2 (including Delta, Omicron, etc.), of which the most dominant mutation has been Omicron. It first appeared in the Republic of South Africa, and the WHO named it B.1.1.529 Omicron and classified it as a variant of concern on November 26, 2021 [25]. In comparison to the Delta variant, the Omicron may highly bind specificity with hACE2, resulting in a higher transmission rate and greater influence on pathogenesis [26]. The common symptoms of COVID-19 are fever, cough, myalgia, fatigue, and headache [27]. In addition to these main symptoms, it may also cause multiple organ dysfunction syndrome (MODS) including neurological symptoms [3,4,28].

2.2. Neurological disorders associated with COVID-19

MODS is one of COVID-19's most distressing symptoms. It refers to a condition in which two or more major organs—namely the heart, lungs, liver, kidneys, and brain—begin to exhibit dysfunctions simultaneously or continuously during treatment, such as in the form of trauma, postoperative shock, or severe infection [3,4,28]. Neurological disorders (stroke, Alzheimer's disease, etc.) have increasingly been identified as consequences of COVID-19. This indicates that there is a growing connection between neurological disorders and COVID-19 [4]. SARS-CoV-2 invades the nervous system through the following two primary mechanisms: First, SARS-CoV-2 interacts with the ACE2 receptor or modifies the tight junction proteins between adjacent brain-blood barrier (BBB) endothelial cells or is phagocytosed by immune cells. It then invades the CNS via a hematogenous or non-hematogenous route. Moreover, it seems reasonable to presume that SARS-CoV-2 travels along the olfactory nerve—the first cranial nerve—from the nasal cavity to the brain for several routes: olfactory epithelium [29] and olfactory nerve [30—32]. In this approach, COVID-19 is being evaluated for its potential to produce a variety of neurological problems, with 'neuroinflammation' as the primary pathology [33].

2.3. The limitations of current approaches to the management of COVID-19

SARS-CoV-2 is widespread today because of its ongoing mutations [1—3]. Several drugs have been developed as treatments for COVID-19, including Paxlovid, Remdesivir, Molnupiravir, and Sotrovimab [34]. In addition to their many beneficial effects, they also have some adverse effects. For example, the most common side effects in Remdesivir studies for COVID-19 include respiratory failure and organ dysfunction, such as low albumin level, low potassium level, low erythrocyte count, and low platelet count, which contribute to blood clot formation and yellow discoloration of the skin [35]. Further, the development of therapeutics is hard, and the long-term stability of current treatments remains unknown [34,36]. Therefore, the combination of vaccination and mask wearing has been the only precaution raised thus far. However, no one knows how vaccination will affect people decades from now. In the absence of specific medications for COVID-19, accumulating studies reported on the possibility that herbal medicine could be used for the prevention and treatment of COVID-19 [14,17].

3. SARS-CoV-2-induced neurological disorders with NLRP3 inflammasome

3.1. The NLPR3 inflammasome and its activation mechanism

Inflammasome activation plays an important role in pathogen defense, primarily inflammation. It promotes an adaptive immune response by assisting in the removal of damaged host cells [6,7]. Researchers have indicated that proper inflammasome activation displays a major role in homeostatic regulation and disease development. NLRP3, one of the main inflammasomes, is composed of an N-terminal pyrin domain, a central nucleotide-binding domain, and a C-terminal leucine-rich repeat domain. NLRP3 has been demonstrated to be an NLR that generates inflammasomes and detects a wide range of viral and endogenous DAMPs, which contain microbial cell wall components, nucleic acids, pore-forming toxins, crystalline environmental agents such as silica, and endogenous compounds including adenosine triphosphate (ATP) and uric acid crystals [6,7,37]. Since the NLRP3 inflammasome can assemble in response to a wide range of DAMPs, it may detect a common cellular distress signal generated by numerous molecules rather than directly interacting with each one [6,7,37]. Changes in cell volume, lysosome rupture, the formation of reactive oxygen species (ROS), K^+ efflux, and Ca^{2+} signaling are considered to be NLRP3 distress signals [6,7,37].

NLRP3 inflammasomes are multimeric protein complexes that are typically consist of a sensor (NLRP3), an adaptor molecule ASC [apoptosis-associated speck-like protein containing a caspase-activation and recruitment domain (CARD)], and an effector cysteine protease procaspase-1 (caspase 1) [6,7,37]. Following activation by immune and inflammatory stimuli, the NLRP3 inflammasome is expressed initially in immune and inflammatory cells, such as microglia, macrophages, neutrophils, mast cells, etc. [6,7,37]. NLRP3 inflammasome is assembled by a diverse range of stimuli and ligands, including PAMPs, such as exogenous microbial molecules and bacterial lipopolysaccharide (LPS), and DAMPs, such as high mobility group box 1, S100 proteins, ATP, IL-33, and monosodium urate [6,7,37].

The assembling procedure of NLRP3 inflammasome involves two phases: priming and activation (Fig. 1). The first step—the priming phase—is triggered primarily by the signaling of pattern recognition receptors, such as the activation of toll-like receptors (TLRs) and cytokine receptors (e.g., tumor necrosis factor receptor (TNFR), which subsequently leads to the transcriptional activation of NLRP3, pro-IL-1β, and pro-IL-18 via nuclear factor kappa B (NF-κB)-mediated transcriptional regulation [38,39]. Two downstream adaptor molecules of TLRs, MyD88 and TIR-domain-containing adapter-inducing interferon-β (TRIF), control the activation of NLRP3 and pro-IL-1β transcription in response to TLR ligands during the priming phase. However, recent reports have demonstrated that the priming phase of NLRP3 inflammasome activation is quite complicated, as it involves both transcriptional and post-translational mechanisms and also requires numerous protein binding partners [38,39]. Meanwhile, the second step involves the assembly of NLRP3 with ASC into the inflammasome complex, and it is initiated by the stimulation of NLRP3 by a plethora of stimuli, including ionic flux (Ca^+ influx, K^+ efflux, Na^+ influx, and Cl^- efflux), ROS, mitochondrial dysfunction, ATP, lysosomal damage, and subsequent activation of pro-caspase-1 with autocatalytic activity [38,39] (Fig. 1) . The active caspase-1 ultimately cleaves pro-IL-1β and pro-IL-18, thus leading to maturation and release of IL-1β and IL-18 with proinflammatory actions [38,39]. The dysregulation of NLRP3 inflammasome has been shown to be associated with various pathological situations, including autoimmune diseases, neurodegenerative diseases, chronic pain, diabetes, and atherosclerosis [38,39]. More recently, an increasing number of studies suggests that NLRP3 inflammasome is dysregulated in neurological conditions and contributes to the pathogenesis of neurological disorders associated with COVID-19 [40,41].

3.2. Neuroinflammation

Neuroinflammation, which refers to a wide spectrum of immune responses in the CNS, is typically closely associated with the status of the neuronal cells, neuroglia (microglia, astrocyte, and oligodendrocyte), and BBB in the CNS [42]. The main cells that participate in neuroinflammation, such as microglia and astrocytes, may be affected by peripheral inflammation [42]. Microglia, which are the resident macrophage-like cells of the CNS, are derived from yolk-sac myeloid progenitors during the early stage of embryonic development [43]. They continually monitor and survey the CNS environment under resting conditions and contribute to its development, neuroprotection, and maintenance of the hemostasis as the first and main form of active immune defense in the CNS [42]. Microglia can be categorized into classical (M1) and alternative (M2) types, and they can be transited from one phenotype to another [44,45]. M1 microglia secrete inflammatory mediators, such as IL-1β, IL-6, IL-12, IL-23, TNF-α, NF-κB, signal transducer and activator of transcription 3 (STAT3), and free radicals such as ROS, induce inflammation and neurotoxicity. Meanwhile, M2 microglia release anti-inflammatory mediators, such as IL-4, IL-10, IL-13, and transforming growth factor-β, induce anti-inflammatory and neuroprotectivity. Microglia-mediated neuroinflammation is considered to be a double-edged sword, as it has both beneficial and harmful effects in neurodegenerative disorders. Accumulating studies have shown that balancing microglia M1/M2 polarization is a promising therapeutic approach in neurodegenerative diseases [44,45]. Typically, the BBB—a highly selective semipermeable border of endothelial cells—divides the CNS from the periphery immune system. However, it can also transport pro-inflammatory mediators produced from the periphery into the CNS [42,46]. The neuroinflammatory response may induce synaptic dysfunction, neuronal death, and a worsening of various pathological events inside the CNS [42,46].

3.3. NLRP3 inflammasome in neurological diseases

The NLRP3 inflammasome, which is a critical innate immune sensor for danger signals, can be activated in the pathogenetic status of neurological disorders, thus resulting in so-called chronic neuroinflammation. The role of NLRP3 inflammasome in neuroinflammation is related to the advancement of various neurological disorders, such as AD, Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS) [8,40,47]. In some pathological environments, the misfolded protein serves as a second messenger to aggregate NLRP3 multimeric protein complex as well as an early signal molecule to initiate transcription and expression of NLRP3 and IL-1β, leading to an inflammatory cascade in a positive feedback loop manner. The NLRP3 inflammasomes generated by another misfolded protein—i.e., mutant superoxide dismutase 1—have been considered to cause neurodegenerative disorders [8,40,47]. Further, the misfolded proteins may affect the endoplasmic reticulum of cells, thereby triggering NLRP3 activation signals by diverse stimuli, and they may also affect multiple molecular and cellular events, including ionic flux, mitochondrial dysfunction, and the production of ROS, while also causing lysosomal damage in chronic disorders like PD [8,40,47,48]. Likewise, in some neuropathological contexts, neuroinflammation may be detrimental to the host [44,45]. Excessive activation of NLRP3 inflammasome can contribute to the development of pathological neuroinflammation by causing excessive cytokine/chemokine release, vascular blockage, dysregulation of BBB, and enhanced infiltration of peripheral immune cells [8,40,47]. As a result, the forms of neuroinflammation induced by COVID-19, including stroke and MS, are mostly mediated by NLRP3 inflammasome.

3.4. SARS-CoV-2 induced neurological disorders with NLRP3 inflammasome

There are at least four possible pathogenic mechanisms that may account for the negative effects of COVID-19 on the nervous system: (1) direct viral encephalitis, (2) systemic inflammation, (3) peripheral organ dysfunction (liver, kidney, lung, etc.), and (4) cerebrovascular changes. Further, neurological manifestations of COVID-19 may arise from most cases as well as a combination of the above [49]. Inflammatory response (inflammation) is the basis of numerous physiological and pathological processes of neurological manifestations associated with COVID-19 [8,40,47]. For inflammation, infection, and tissue damage, it is known that leukocytes and plasma proteins migrate to the injured tissue location [50]. To facilitate tissue repair and remodeling, inflammation helps eliminate and manage the causes, such as through phagocytosis and activation of the inflammasome, which promotes apoptosis [51]. However, an overactive inflammatory response can cause induce tissue damage [44,45].

Severe COVID-19 cases result in acute respiratory distress syndrome with systemic inflammation, wherein lung injury is related to secretion of inflammatory cytokines IL-6 and IL-1β [1–3,52]. Systemic inflammatory syndrome is characterized by aberrantly regulated proinflammatory cytokine cascades triggered by an intense, rapid overregulation of the innate immune response. COVID-19 severity is related to enhanced proinflammatory

cytokines and chemokines and IL-6 in particular is predictive of COVID-19 fatality [52]. High levels of IL-1β and IL-6 have been confirmed in autopsy tissues of SARS-CoV patients [53], and single cell RNA-seq analysis of peripheral blood in COVID-19 patients has shown increased subsets of $CD14^+$ IL-1β-producing monocytes [1–3,52]. However, a clear mechanism of this is yet to be understood. The inflammatory basis underlying COVID-19 fatality means that the development of immunoregulatory factors is of paramount importance. There is significant literature implicating the NLRP3 inflammasome as well as cytokine storm in this pathogenesis [8,40,47,48]. The NLRP3 inflammasome is an important cause of activation of the innate immune system to recognize pathogens, including viral infections [8,40,47,48]. SARS-CoV 3a protein activates the NLRP3 inflammasome in LPS-primed macrophages with 3a-mediated IL-1β secretion associated with K^+ efflux and mitochondrial ROS [54].

4. P. ginseng as a potential therapeutic for neurological disorders associated with COVID-19; toward targeting inflammasome

4.1. Rationale for considering natural products as potential therapeutics for COVID-19

The medications mentioned above can offer some relief in the pandemic situation. However, the pandemic situation may still be exacerbated by continued mutation of the virus, which could lead to drug-resistant mutants. Further, the developed anti-viral drugs might not be effective for viral mutations since most of them target specific viral proteins [55]. Thus, researchers have considered there to be a rationale for considering safer and more effective therapeutics for COVID-19 by looking at natural products. Many evidences have therefore been conducted on the anti-viral effects of herbal medicines and natural products such as P. ginseng [18]. Briefly, abundant studies have demonstrated that natural products have some potential in targeting viral life cycle, virus–host specific interactions, and cytokine storm [12,56]. Recent evidences have shown that NLRP3 inflammasome is an attractive pathological mechanism for neurological disorders associated with COVID-19, and that P. ginseng is a potential regulator for NLRP3 inflammasome.

4.2. P. ginseng and its effect to the mechanism of neuroinflammation

P. ginseng, which is mostly found in Asian countries, is a well-known traditional medicinal herb with a long history of usage [57–60]. P. ginseng has anti-inflammatory, anti-oxidation, anti-aging, anti-neurodegenerative, and restorative activities as well as memory and cognitive enhancing activities with less side effects than alternative options [57–60]. Impressively, P. ginseng has been revealed to increase the ability to defend against influenza in both clinical trials and in vivo experiments and the ability to defend against pneumococcal pneumonia in in vivo experiments [61]. Based on these findings, P. ginseng may help provide immunity against COVID-19 [61]. Although there has been no study examining ginseng with inflammasome in the specific context of COVID-19, recent studies have indicated that P. ginseng has the potential to deal with various neurological disorders such as aging, recognitive dysfunction, and stroke by regulating inflammasome mechanisms [62–64]. Therefore, in this review, we will discuss the potential therapeutic usage of P. ginseng for neurological disorders caused by COVID-19 through controlling inflammasomes and suggest future research directions.

4.3. Possibility of using ginseng for SARS-CoV-2-induced neurological disorders with NLRP3 inflammasome

4.3.1. Ginseng extract

Ginseng extract contains both saponins (ginsenosides) and non-saponins (saccharides, nitrogen-containing compounds, fat-soluble components, vitamins, and ash). Since ginseng extract has various physiological and pharmacological activities, it has been widely used as both an energy-enhancing agent and an immunostimulant for healthy persons and as a traditional medicine to treat multiple pathological statuses such as infectious and inflammatory diseases [65,66]. Ginseng was first reported to have an effect on inflammasome activation in 2014 [67]. In that report, Korean Red Ginseng (KRG) extract (KRGE) was shown to block the production of IL-1β and caspase-1 (p20), and the formation of ASC pyroptosome resulting from NLRP3 inflammasome activation was shown to trigger, in a dose-dependent manner, (ATP and nigericin)-induced human monocyte-like cells line (THP-1) and mouse bone marrow-derived macrophages (BMDMs) [67]. Further, KRGE significantly reduced the lethality caused by endotoxemia in LPS-induced C57BL/6 mice [67] (Table 1).

4.3.2. Saponin fraction and its components

Ginseng saponins (ginsenosides or panaxosides) are a class of natural product steroid glycosides, and triterpene saponins are the main active compounds found in the plant genus Panax (ginseng) [18]. The saponins and their metabolites, including 27 proto-panaxadiol-, 14 protopanaxatriol-, and 2 oleanane-type ginsenosides, are responsible for various pathological statuses, including neurological, cardiovascular, metabolic, immunological, and inflammatory diseases, via their biological and pharmacological activities [65,66]. Interestingly, recent studies have focused on their regulatory functions on the activation of inflammasomes in inflammation [6,7,11] (Table 1). However, there is still little known about their pharmacological roles and the underlying molecular mechanisms in neurological disorders associated with COVID-19.

Saponin fraction; When saponin fraction (rich in ginsenosides) in the priming and activation stages of NLRP3 inflammasome in NLRP3 triggers (ATP and nigericin)-induced BMDMs, the saponin fraction inhibits the enhancement of NLRP3 and pro-IL-1β transcription and translation at the priming step [20]. It has also been shown to reduce the production of IL-1β and caspase-1 (p20) as well as the formation of ASC pyroptosome during the activation step [20]. The results suggest that the ginseng saponin may contribute to inhibiting both the priming and activation of NLRP3 inflammasome activation. Microglia-mediated inflammatory events play an important role in aging-associated neurodegenerative disorders [42,44,45]. The TXNIP/NLRP3 pathway is a key pathway producing to microglial activation [68]. Research has shown that saponins from P. notoginseng treatment improve aging-related neuronal damage and neuroinflammation by ameliorating TXNIP-mediated NLRP3 inflammasome activation in cortex and hippocampus from aged Sprague-Dawley rats, and that LPS and ATP co-stimulated BV2 microglia [69]. Obesity can lead to behavioral alterations such as cognitive dysfunction and depression-like behaviors in both humans and rodents [70]. Saponins from P. japonicus treatment have been shown to alleviate high-fat diet (HFD)-induced recognitive impairment and depression-like behaviors in HFD-fed Balb/c mice, which could partly be due to the ability of saponins from P. japonicus to mitigate neuroinflammation through inhibition of NLRP3 inflammasome (NLRP3, caspase-1, ASC, and IL-1β) and upregulation of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors signaling pathway [71]. Saponin fraction of KRG reveals an anti-inflammatory effect by ameliorating the mRNA expression of

Table 1
Regulating roles of ginseng and ginseng-derived materials on NLRP3 inflammasome

Materials	Effects	Mechanisms	Assay models	Ref.
KRG extract	Anti-inflammation	(↓) NLRP3 inflammasome (IL-1β, ASC, and caspase-1)	ATP/nigericin-induced BMDMs and THP-1 cells; LPS-induced C57BL/6 mice	[67]
Saponin from KRG	Anti-inflammation; Anti-oxidation	(↓) NLRP3 inflammasome (Nlrp3, Asc, pro-IL-1β, IL-1β, pro-caspase-1, and caspase-1)	Ovaries of aged C57BL/6 mice (12M)	[72]
Saponins from P. notoginseng	Anti-inflammation	(↓) NLRP3 inflammasome (NLRP3, ASC, IL-1β, caspase-1, and TXNIP); (↓) Microglial activation; (↓) Number of degenerated neurons	Cortex and hippocampus from aged SD rats (24M); LPS/ATP-co-stimulated BV-2 cells	[69]
Saponins from P. japonicus	Improvement of recognitive impairment, Anti-depressant; Neuroprotection; Anti-inflammation	(↓) NLRP3 inflammasome (NLRP3, ASC, IL-1β, and caspase-1) (↑) AMPA receptors signaling pathway	Cortex and hippocampus from HFD-fed Balb/c mice (6M)	[71]
Ginsenoside Rd	Anti-inflammation; Alleviation of body weight loss	(↓) NLRP3 inflammasome (IL-1β and caspase-1); (↓) Mitochondrial translocation of p62 and mitophagy; (↓) Pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) in both serum & colonic tissues; (↓) Colonic pathological damage (with lower MPO, iNOS activities, and higher GSH level)	DSS-induced murine colitis model (C57BL/6); THP-1 cells	[73]
	Neuroprotection; Anti-oxidation	(↑) Neurological function; (↓) infarct volume; (↓) brain water content (↑) miRNA-139-5p; (↓) FoxO1; (↑) Keap1 and Nrf2; (↓) Pyroptosis (ROS/TXNIP/NLRP3)	MCAO/R-induced C57BL/6 mice; OGD/R-induced primary cortical neurons	[63]
	Neuroprotection	(↑) Neurological deficits, glucose uptake, and infarct size; (↓) NLRP3 inflammasomes (NLRP3, cleaved caspase-1, cleaved IL-1β, and gasdermin D); (↓) Pyroptosis (active caspase-1⁺/TUNEL⁺ cells); (↓) Drp1-mediated mitochondrial fission (expression of Drp1)	OGD/R-induced BV-2 cells	[64]
Ginsenoside Re	Enhancement of memory impairment; Neuroprotection	(↓) Neuronal loss; (↑) BDNF, Nrf2, HO-1, synaptophysin, and PSD-95; (↓) NLRP3 (ASC and caspase-1)	Hippocampus of CRS-induced C57BL/6J mice	[74]
Ginsenoside Rg1	Anti-inflammation	(↓) NLRP3 inflammasomes (NLRP3, ASC); (↓) Microglia pyroptosis (propidium iodide-positive cells, pro-caspase-1, cleaved caspase-1, IL-1β, mature IL-1β, gasdermin D, and gasdermin D-S); (↓) p-STAT3	LPS-induced BV-2 cells; Brain from SD rats aged 3 days	[78]
	Anti-inflammation; Anti-depression	(↓) NLRP3 inflammasomes (NLRP3, ASC, and caspase-1) (↓) IL-1β, IL-6, and TNF-α; (↓) p−NF−κB	PFC of CUM stress-induced rats	[77]
Ginsenoside Rg3	Anti-endotoxin	(↓) NLRP3 inflammasome (S-nitrosylation); (↓) iNOS and NO; (↑) Survival time	LPS-induced endotoxic shock model in C57BL/6 mice	[80]
		(↓) IL-1β and caspase-1; (↓) NLRP3 inflammasomes (NLRP3); (↓) NEK7-NLRP3 and NLRP3-ASC interaction, ASC oligomerization, and speckle formation	J774.A1, RAW264.7, HEK293T, BMDMs, and THP-1 cells; LPS-induced C57BL/6J mice	[79]
Ginsenoside Rh1	Anti-inflammation	(↓) IL-1β	Nigericin/dsDNA induced mouse/human macrophages	[67]
Compound K	Enhancement of cognitive dysfunction; Anti-inflammation; Antioxidant	(↓) NLRP3 inflammasome (NLRP3, ASC, cleaved caspase-1, mature IL-1β, and TXNIP); (↓) ER stress (BiP, CHOP, p-ERK, p-IRE1α, and ATF6)	Hippocampus of db/db mice	[82]
Notoginsenoside R1	Enhancement of cognitive dysfunction; Anti-depressant; Anti-inflammation; Antioxidant	(↓) Oxidative stress (SOD, MDA, and protein carbonyl); (↑) Akt/Nrf2 pathway (Akt, p-Akt, Nrf2, HO-1, and TXNIP); (↓) NLRP3 inflammasome activation (NLRP3, ASC, and IL-1β)	Hippocampus of db/db mice; high-glucose-treated HT22 cells	[83]
Pseudoginsenoside-F11	Enhancement of cognitive dysfunction; Neuroprotection; Anti-inflammation	(↓) Neuronal loss and microglial activation; (↓) NLRP3 inflammasome (NLRP3); (↓) Accumulation of AGEs and expression of RAGE; (↓) H₂O₂ and MDA; (↑) GSH; (↓) Nrf2 and GST	Hippocampus of D-galactose-treated C57BL/6 mice	[84]
Nonsaponin fractions of KRGE	Anti-inflammation	(↑) NLRP3 inflammasome; (↑) Proinflammatory cytokines (pro-IL-1β and TNF-α); (↑) Anti-inflammatory cytokine (IL-10); (↑) TLR4/NF-κB signaling pathway; (↑) Peritoneal IL-1β and IL-6	ATP/nigericin-induced BMDMs and THP-1 cells; LPS-induced C57BL/6 mice	[86]
	Anti-inflammation	(↓) Peritoneal cytokines (IL-1β, IL-6, IL-10, and TNF-α) (↓) IL-1β and NLRP3 transcription via TLR 4 signaling	Peritoneal exudate cells; MDMs	[87]
Gintonin-Enriched Fraction	Anti-inflammation	(↓) p-p38 and p-ERK; (↓) NLRP3 inflammasome; (↓) Inflammatory cytokines (IL-6 and IL-18); (↓) Oxidative stress (GSH reductase and catalase)	High temperature stress-stimulated C2C12 cells	[93]
Fructose-arginine	Anti-inflammation	(↓) AIM2 inflammasomes (IL-1β); (↓) NLRP3 or NLRC4 inflammasomes	Murine BMDMs and THP-1 cells	[21]
Combination of P. ginseng and Angelica sinensis	Anti-inflammation; Neuroprotection	(↑) Neurological deficits, glucose uptake, and infarct size; (↓) NLRP3 inflammasomes (NLRP3, pro-caspase-1, cleaved caspase-1, pro-IL-1β, and cleaved IL-1β); (↓) Microglial pyroptosis (active caspase-1+/TUNEL+/Iba-1+)	MCAO/R-induced SD rats; OGD/R-induced BV-2 cells	[94]
Renshen Shouwu extract	Anti-inflammation; Neurogenesis; Angiogenesis	(↑) Newborn neurons and brain microvessel; (↑) Inflammatory signaling (TLR4, p−NF−κB p65, NLRP3, pro-IL-1β, IL-1β, pro-caspase-1, caspase-1)	MCAO/R-induced SD rats	[95]

Abbreviations: AGEs, advanced glycation endproducts; Akt, protein kinase B; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ATF6, activating transcription factor 6; ATMs, adipose tissue macrophages; ATP, adenosine triphosphate; BDNF, brain-derived neurotrophic factor; BMDMs, bone marrow-derived macrophages; CHOP, gene encoding the C/EBP homologous protein-10; CRS, chronic restraint stress; CUM, chronic unpredictable mild stress; DSS, dextran sulfate sodium; ER, endoplasmic reticulum; GSH, glutathione; GST, glutathione S-transferase; HFD, high-fat diet; IL, interleukin; HO-1, heme oxygenase-1; iNOS, inducible nitric oxide synthase; Keap1, Kelch-like ECH-associated protein 1; KRG, Korean Red Ginseng; KRGE, KRG extracts; LPS, lipopolysaccharide; MDA, malondialdehyde; MCAO, middle cerebral artery occlusion; MCAO/R, middle cerebral artery occlusion/reperfusion; MDA, malondialdehyde; MDMs, monocyte-derived macrophages; miRNA, microRNA; MPO, myeloperoxidase; MSU, mono-sodium urate; NEK7, NIMA Related Kinase 7; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRC4, NLR family CARD domain containing 4; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; Nrf2, Nuclear factor erythroid-2-related factor 2; OGD/R, oxygen ogrglucose deprivation/reoxygenation; p-IRE1α, phospho-inositol-requiring transmembrane kinase endoribonuclease-1α; p-ERK, phospho-extracellular signal-regulated kinase; PFC, prefrontal cortex; PSD-95, postsynaptic density protein-95; RAGE, receptor of advanced glycation endproducts; ROS, reactive oxygen species; SD, Sprague-Dawley; SOD, superoxide dismutase; THP-1, a human monocytic cell line derived from an acute monocytic leukemia patient; TLR, toll-like receptor; TNF-α, tumor necrosis factor-α.
TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labeling; TXNIP, thioredoxin interacting protein.

genes encoding NLRP3 inflammasome components (Nlrp3, Asc, pro-IL-1β, IL-1β, pro-caspase-1, and caspase-1) in cultured ovaries from aged C57BL/6 mice [72] (Table 1). Taken together, these findings indicate that saponin fraction may be used as a potential agent for the treatment of infection and inflammation-related neurological diseases.

Ginsenosides; Ginsenoside Rd—a monomer component of *P. ginseng* and *P. notoginseng*—has been shown to enhance neurological function with reduction of infarct volume and brain water content by upregulating microRNA-139-5p (miR-139-5p) to inhibit FoxO1, which controls Keap1 transcriptional activity, and subsequently activates the nuclear factor-erythroid 2-related factor2 (Nrf2) antioxidant pathway, thus resulting in alleviation of ROS/TXNIP/NLRP3 inflammasome axis-driven pyroptosis in a middle cerebral artery occlusion/reperfusion (MCAO/R) model in male C57BL/6 mice and oxygen-glucose deprivation/reoxygenation (OGD/R) model in primary cortical neurons [63]. Microglia are considering as pivotal regulators of neuronal function and behavior in nearly every area of neuroscience, including stroke research [62]. Ginsenoside Rd reduced OGD/R-induced BV-2 microglial cell damage through the suppression of NLRP3 inflammasomes activation (NLRP3, cleaved caspase-1, cleaved IL-1β, and gasdermin D) and pyroptosis (active caspase-1+/TUNEL+ pyroptotic cells) by inhibiting dynamin-associated protein 1-mediated mitochondrial fission (expression of dynamin-related protein 1) [64]. Further, ginsenoside Rd exhibited protective effects such as alleviation of body weight loss, colon length shortening, and colonic pathological damage with lower myeloperoxidase and inducible nitric oxide synthase (iNOS) activities and higher glutathione levels in dextran sulfate sodium-stimulated murine colitis. Its positive effects were found to be associated with the production of pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) in both serum and colonic tissues as well as the inactivation of p62-driven mitophagy-mediated NLRP3 inflammasome (caspase-1 production and IL-1β secretion) in colonic tissues and human THP-1 cells [73] (Table 1).

Ginsenoside Re is a triterpene saponin that exhibits various pharmacological roles including antidepressant, anti-inflammatory, antioxidative, neuroprotective, and immunostimulatory activities [74]. A recent study has found that ginsenoside Re protects cognitive deficits by inhibiting the down-regulation of brain-derived neurotrophic factor, Nrf2, heme oxygenase (HO)-1, synaptophysin, and postsynaptic density protein-95, as well as the upregulation of NLRP3, ASC, and caspase-1 in the hippocampus of CRS-treated mice [75] (Table 1).

Ginsenoside Rg1 is a steroid glycoside that possesses a broad spectrum of pharmacological properties like neuroprotective, antidepressant, anti-inflammatory, and immune modulatory effects [76]. Ginsenoside Rg1 has been shown to alleviate depression-related behaviors (locomotor activity and immobile time) in rats that have been exposed to chronic unpredictable mild stress by inhibiting pro-inflammatory cytokine IL-1β-related neuro-inflammation via regulating NF-κB signaling (p–NF–κB) and the NLRP3 pathway (NLRP3, ASC, and caspase-1) [77]. Ginsenoside Rg1 has also been shown to inhibit microglia pyroptosis (propium iodide-positive cells, pro-caspase-1, cleaved caspase-1, IL-1β, mature IL-1β, and gasdermin D) and the production of inflammasomes (NLRP3, ASC) by regulating STAT3 signaling in LPS-stimulated BV-2 microglia cells and the corpus callosum of postnatal brain [78] (Table 1). These results indicate that ginsenoside Rg1 could play a role in mitigating depression-related behaviors through inhibiting both the NLRP3 inflammasome and microglia pyroptosis.

Ginsenoside Rg3, a naturally occurring compound, has been shown to protect mice from lethal endotoxic shock by blocking IL-1β secretion and caspase-1 activation through inhibiting LPS priming and specifically inhibiting the activation of the NLRP3 inflammasome and not the NLRC4 (NLR family CARD domain containing 4) or AIM2 (absent in melanoma 2) inflammasomes in human and mouse macrophages [79]. Ginsenoside Rg3 abrogated NEK7-NLRP3 interaction and subsequently inhibited its assembly (NLRP3-ASC interaction, ASC oligomerization, and speckle formation). More importantly, ginsenoside Rg3 reduced IL-1β production induced by LPS in mice [79] (Table 1). Taken together, these findings suggest that ginsenoside Rg3 could inhibit endotoxic shock via downregulating the NLRP3 inflammasome.

Compound K, a secondary ginsenoside bio-transformed from major ginsenosides, is more bioavailable and soluble than its original ginsenosides [80]. Compound K has been shown to improve behavioral and cognitive dysfunction in diabetic db/db mice by inhibiting oxidative stress and inflammatory response in hippocampal tissue [81]. Its positive effects were specifically associated with the alleviation of the NLRP3 inflammasome pathway, as demonstrated by the reduced expression of thioredoxin interacting protein (TXNIP), NLRP3 inflammasomes, ASC, cleaved caspase-1, and mature IL-1β in the hippocampus of db/db mice. It also reduced endoplasmic reticulum (ER) stress via suppressing the levels of BiP, CHOP, p-extracellular signal-regulated kinase (ERK), p-inositol-requiring transmembrane kinase endoribonuclease-1α, and activating transcription factor 6 in the hippocampus [81] (Table 1). These results suggest that compound K improves behavioral and cognitive dysfunction, potentially by ameliorating oxidative stress and inflammatory event and regulating the NLRP3 inflammasome pathway and ER stress.

Notoginsenoside R1, one major component of P. notoginseng, has been shown to both improve cognitive dysfunction, depression-like behaviors, and inflammation in db/db mice and decrease the oxidative stress (superoxide dismutase, malondialdehyde, and protein carbonyl) in the hippocampal neurons of the same mice [82]. It also activated the protein kinase B (Akt)/Nrf2 pathway (Akt, p-Akt, Nrf2, HO-1, and TXNIP) and inhibited NLRP3 inflammasome activation (NLRP3, ASC, and IL-1β) in the hippocampal neurons [82]. However, these positive activities of notoginsenoside R1 were found to be abolished by pretreatment with the phosphatidylinositol 3-kinase inhibitor LY294002 [82] (Table 1).

Pseudoginsenoside-F11, an ocotillol-type saponin from *P. quinquefolium* [83], alleviated d-galactose-induced cognitive impairment associated with the attenuation of the loss of neurons and the over-activation of microglia in hippocampus [84]. Its positive activities were also related to the reduction in the levels of NLRP3 inflammasome through reducing the accumulation of advanced glycation endproducts and the expression of the receptor of advanced glycation endproducts in the hippocampus of d-gal-treated mice [84]. In a recent study, ginsenoside Rh1—a tetracyclic triterpenoid—attenuated IL-1β secretion induced by a NLRP3 trigger (nigericin or dsDNA) in mouse and human macrophages [67] (Table 1).

4.3.3. Non-saponin fraction and its components

The non-saponins of ginseng include saccharides (monosaccharide, disaccharide, trisaccharide, polysaccharides, crude fiber, pectin, etc.), nitrogen-containing compounds (proteins, peptides, amino acids, nucleic acids, and alkaloids), fat-soluble components (lipids, fatty acids, polyacetylenes, phenolic compounds, essential oils, phytosterols, organic acid, and terpenoid), water-soluble vitamins, and ash [65]. The non-saponins have various physiological and pharmacological features, such as anti-inflammatory and antiviral activities [65]. Recent studies have shown that non-saponin and its components may regulate the

activation of inflammasome in various pathological environments [19–23] (Table 1).

When non-saponin fraction (which is higher in acidic saccharide content) in the priming and activation step of NLRP3 inflammasome in NLRP3 triggers (ATP and nigericin)-induced BMDMs, the non-saponin fraction upregulates gene expression (mRNA of pro-IL-1β) for NLRP3 inflammasome activation via activation of the TLR4/NF-κB signaling pathway during the priming step [85], while it does not attenuate the production of IL-1β and caspase-1 (p20) or the formation of ASC pyroptosome in the activation step [85] (Table 1).

When mice were fed non-saponin for 7 days and peritonitis was induced, non-saponin ingestion attenuated the production of peritoneal cytokines (IL-1β, IL-6, IL-10, and TNF-α) and the TLR transcription levels in peritoneal exudate cells compared to those of the control group [86]. Related to this, BMDMs treated with non-saponin showed downregulation of TLR4 mRNA and protein expression, which was regulated by the TLR4-MyD88-NF-κB signal pathway [86] (Table 1).

When mouse BMDMs, THP-1, and a murine model were transfected with dsDNA or inoculated with *Listeria monocytogenes*, the non-saponin fraction and saponin-eliminating fraction of KRGE were found to selectively attenuate the activation of AIM2 inflammasomes (IL-1β), but not that of NLRP3 or NLRC4 inflammasomes [21]. Further, fructose-arginine—an amino-sugar—has also been shown to be effective against AIM2 inflammasome activation [21] (Table 1).

Gintonin, when isolated from ginseng, has been shown to act as a ginseng-derived lysophosphatidic acid (LPA) receptor ligand and elicit the $[Ca^{2+}]_i$ transient through six LPA receptors (LPARs) [87–89]. The LPARs are expressed on most cell types within central and peripheral nervous tissues, and they have been functionally related to many neural processes and pathways involved in health and pathological status, including those involved in COVID-19 [90,91]. Gintonin-enriched fraction (GEF), a non-saponin component, is composed of a large amount of lysophosphatidic acids as a functional group and contains a large amount of linoleic acid and phosphatidic acids, which are lipid components [87–89]. A recent study demonstrated that GEF may inhibits heat stress-induced inflammation through LPARs [92]. In the high temperature stress-stimulated C2C12 cells (a subclone of myoblasts), GEF treatment was shown to suppress the phosphorylation of p38 and ERK, the secretion of inflammatory cytokines such as IL-6 and IL-18, and the expression of glutathione reductase and catalase related to oxidative stress [92]. Meanwhile, the beneficial effects of GEF were associated with suppressive expression of inflammatory agents such as NLRP3 inflammasome through LPARs [92] (Table 1).

4.3.4. Modified types based on P. ginseng and its ingredients

As common traditional Chinese herbal medicines, the combination of P. *ginseng* and Angelica sinensis (CPA) has been used to treat stroke for a thousand years, and it has been shown to have satisfactory clinical efficacy in various neurological disorders [93]. The combination of CPA and MCC950 (NLRP3-specific inhibitor) has been shown to improve neurological deficits, glucose uptake, and infarct size associates with the attenuation of the activation of NLRP3 inflammasomes (NLRP3, pro-caspase-1, cleaved caspase-1, pro-IL-1β, and cleaved IL-1β), microglial pyroptosis (active caspase-1+/TUNEL+/Iba-1+), and related signaling pathways in infracted tissue of MCAO rats [64]. Further, treatment with ginsenoside Rd and Z-ligustilide has been shown to suppress high expression of dynamin-related protein 1 and mitochondrial fission, as well as NLRP3 inflammasomes activation and pyroptosis in OGD/R-induced BV2 cells [64]. Renshen Shouwu (RSSW), which is composed of P. *ginseng* and fleece flower root (Polygonum

multiflorum Thunb.), is a traditional Chinese medicine that is beneficial in the prevention of neurasthenia, forgetfulness, insomnia, inappetence, and excessive fatigue [94]. Research has shown that it increases neurogenesis (the number of newborn neurons) and angiogenesis (brain microvessel density) after ischemic stroke via inhibition of the TLR4/NF-κB/NLRP3 inflammatory signaling pathway (TLR4, p–NF-κB p65/p65, NLRP3, pro-IL-1β, IL-1β, pro-caspase-1, and caspase-1 proteins) in MCAO-induced rats [94] (Table 1). These studies indicate that certain combinations including P. *ginseng*-derived substances as a main component may be candidate treatments for neurological disorders that are associated with COVID-19 and linked with the regulation of NLRP3 inflammasome.

5. Discussion and conclusions

The COVID-19 pandemic has necessitated enormous efforts to discover effective and safe therapeutics to target all stages of multiple organ damage, including various neurological manifestations that affect both the central and peripheral nervous systems [34–36]. However, the scope of research activities, strict scientific ethics, pathological mechanism, and clinical value have made it difficult to keep up with the rapidly evolving COVID-19 environment [34–36]. Further, most researchers examining promising candidate drugs have given up on them based on the results obtained in the later phases of clinical trials [34–36]. Thus, there are currently no known specific therapeutics that can inhibit SARS-CoV-2 infection and cure MODS including the neurological symptoms caused by the infection. Since there are no definite therapeutics, natural products such as ginseng-derived substances are widely used as immunostimulators or health supplements to prevent SARS-CoV-2 infection and minimize the symptoms of COVID-19 [34,36].

Accumulated evidence has shown that COVID-19 clearly activates NLRP3 inflammasomes in the nervous system during SARS-CoV-2 infection, and these inflammasomes are closely related to the severity of various neurological disorders such as stroke and depression [8,40,47]. Therefore, agents targeting NLRP3 inflammasome signaling may be attractive drugs for curing neurological disorders associated with COVID-19. At the early stages of the neuroinflammatory responses caused by SARS-CoV-2 infection, alleviating the level of inflammatory response including the NLRP3 inflammasome activation may substantially inhibit the levels of proliferation, differentiation, recruitment, and infiltration of resident microglia and peripheral immune cells (macrophages, T cell, etc.), which induce MODS including neurological symptoms. Therefore, this therapeutic strategy may be a pivotal step to defend against deterioration of the host's health.

P. *ginseng* has been widely used as a functional food, therapeutic supplement, and medicine in Asian countries including Korea for thousands of years, and it is empirically known to be safe and nontoxic [57–60]. In recent decades, a number of in vitro and in vivo experiments as well as human studies have detailed the safety, toxicity, and other adverse events of various types of ginseng samples and their components [95]. Although there are some cases of patient risk associated with ginseng abuse and misuse depending on patients' conditions, it is generally considered to be a safe herb [95].

P. *ginseng*-derived substances (extract, saponin, non-saponin, and their ingredients) have been shown to be reliable nutraceuticals that prevent the deterioration of multiple inflammatory and infectious diseases by inhibiting all phases (the inducer, sensor, mediator, and lesion phases) of various inflammatory responses [18,57–66]. Recently, several studies have reported that P. *ginseng*-derived substances can impressively prevent the two steps
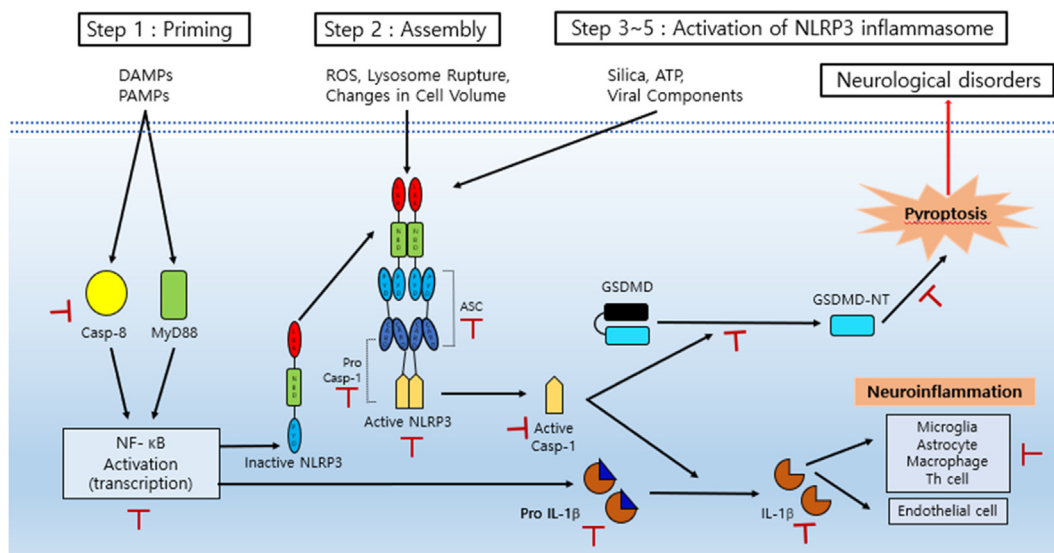
Fig. 1. Molecular mechanisms of NLRP3 inflammasome activation caused by SARS-CoV-2 infection and therapeutic targets by *P. ginseng*-derived substances. The first step is priming, the TLRs−adaptor molecule MyD88 pathway, which stimulates pro-IL-1β and NLRP3 transcription via NF-kB activation. Stimulation of the caspase-8 protein complex by PAMPs or DAMPs can activate NF-kB transcription. The second step is NLRP3 inflammasome assembly. The cytosolic sensor molecule NLRP3, the adaptor protein ASC, and the effector molecule pro-caspase-1 constitute the NLRP3 inflammasome. When pro-caspase-1 turns into caspase-1, active caspase-1 leads to the maturation of IL-1β and promotes pyroptosis, a type of intrinsic inflammatory cell death. The NLRP3 inflammasome in microglia and astrocytes, activated by various external and endogenous stimuli, causes IL-1β maturation and pyroptosis. High levels of IL-1β bind to receptors of glial cells, neurons, macrophages, and endothelial cells. It interacts with other cytokines to activate Th-cell signaling, resulting in the aggravation of the inflammatory cascade within the CNS. Therapeutic targets for controlling NLRP3 inflammasome may be inhibited by *P. ginseng*-derived substances (PG); Red marks designate therapeutic targets where PG exhibit their regulatory effects. ASC, apoptosis-related speck-like protein containing a caspase recruitment domain; ATP, adenosine triphosphate; CARD, caspase activation and recruitment domain; DAMPs, damage-associated molecular pattern molecules; GSDMD, gasdermin D; GSDMD-NT, gasdermin-N domain of GSDMD; IL, interleukin; LRR, leucine-rich repeat NACHT (NOD), nucleotide binding and oligomerization domain; NF-κB, nuclear factor-κB; NLRP3, nucleotide-binding oligomerization domain-, leucine-rich repeat- and pyrin domain-containing 3; PAMPs, pathogen-associated molecular pattern molecules; PYD, pyrin-only domain; Th, T helper.

(priming and activation) in ameliorating NLRP3 inflammasome signaling in several pathological events including neurological disorders [20], and that saponin and non-saponin fractions can differently regulate the priming and activation steps of NLRP3 inflammasome [20]. In other words, the non-saponin fraction has been shown to activate the gene expression (mRNA of pro-IL-1β) for NLRP3 inflammasome activation via activation of the TLR4/NF-κB signaling pathway during the priming step [85], whereas the saponin fraction has been shown to inhibit the enhancement of NLRP3 and pro-IL-1β transcription and translation during the priming step [20]. Regarding the conflicting features of non-saponin and saponin fractions on NLRP3 inflammasome signaling, it might be possible to use *P. ginseng*-derived materials as a functional food to enhance immunity, which may inhibit the initial inflammatory response by virus invasion or reduce the final execution of NLRP3 inflammasome activation. Further, *P. ginseng*-derived substances have been shown to suppress the worsening symptoms of neurological disorders associated with COVID-19 such as stroke, cognitive decline, and depression-like behaviors [63,75,77]. Therefore, if COVID-19 patients regularly take *P. ginseng*-derived materials as a supplement, then they will be less likely to reach emergency signs of severe COVID-19 via control of the hyper-activation of NLRP3 inflammasome signaling. Further, if healthy persons regularly take it, they may block the chance of SARS-CoV-2 infection or alleviate the intensity of the symptoms caused by the infection.

Traditional herbal formulas usually comprise multiple herbs in a single formula. The formulas are expected to show their clinical effects by critical therapeutic roles through "multi-components, multi-targets and multi-pathways" mechanisms [12−17]. Interestingly, certain combinations (CPA and RSSW) including *P. ginseng*-derived substances mitigated neurological symptoms that are related to COVID-19 and associated with the regulation of NLRP3 inflammasome [64,94]. There seems to be a general assumption that the synergistic therapeutic effects of the combinations including *P. ginseng*. However, exploring the interaction among complex mechanisms and components may scientifically demonstrate the critical therapeutic role of *P. ginseng*. Thus, further studies need to be continued to determine potential therapeutic roles (synergistic effects) of herbal formulas including *P. ginseng*-derived substances as a main component.

Taken together, these results indicate that *P. ginseng*-derived materials (extract, saponin, non-saponin, and their components) could represent an effective and safe therapeutic for targeting NLRP3 inflammasome activation to prevent or treat the neurological disorders associated with COVID-19 (Fig. 1). Unfortunately, direct scientific evidence of *P. ginseng*-mediated prevention of SARS-CoV-2 infection and amelioration of COVID-19 symptoms has yet to be reported. Therefore, pharmacological issues of *P. ginseng*-derives substances need to be further studied before it can be recommended as a therapeutic option for COVID-19 patients.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Research Program and Undergraduate Research Assistant Program in Kyung Hee University (2021).

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