Journal of Ginseng Research 46 (2022) 337–347

Contents lists available at ScienceDirect

Journal of Ginseng Research

journal homepage: https://www.sciencedirect.com/journal/journal-of-ginseng-research

Review Article

Can *Panax ginseng* help control cytokine storm in COVID-19?

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ARTICLE INFO

Article history:
Received 3 February 2022
Received in revised form
21 February 2022
Accepted 22 February 2022
Available online 25 February 2022

Keywords:
Coronavirus disease 2019
SARS-CoV-2
Cytokine storm
Panax ginseng
Therapeutic strategies

ABSTRACT

Coronavirus disease 2019 (COVID-19) is currently a pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 are directly associated with hyper-activation of innate immune response that excessively produce pro-inflammatory cytokines and induce cytokine storm, leading to multi-organ-failure and significant morbidity/mortality. Currently, several antiviral drugs such as Paxlovid (nirmatrelvir and ritonavir) and molnupiravir are authorized to treat mild to moderate COVID-19, however, there are still no drugs that can specifically fight against challenges of SARS-CoV-2 variants. *Panax ginseng*, a medicinal plant widely used for treating various conditions, might be appropriate for this need due to its anti-inflammatory/cytokine/viral activities, fewer side effects, and cost efficiency. To review *Panax ginseng* and its pharmacologically active-ingredients as potential phytopharmaceuticals for treating cytokine storm of COVID-19, articles that reporting its positive effects on the cytokine production were searched from academic databases. Experimental/clinical evidences for the effectiveness of *Panax ginseng* and its active-ingredients in preventing or mitigating cytokine storm, especially for the cascade of cytokine storm, suggest that they might be beneficial as an adjunct treatment for cytokine storm of COVID-19. This review may provide a new approach to discover specific medications using *Panax ginseng* to control cytokine storm of COVID-19.

1. Introduction

In late December 2019, Coronavirus Disease 2019 (COVID-19) was first reported in Wuhan, China. Subsequently it has spread worldwide [1]. The World Health Organization (WHO) declared it an outbreak that 'constitutes a Public Health Emergency of International Concern' on January 30, 2020 and characterized it as a pandemic on March 11, 2020 [1]. Thus, COVID-19 is a major threat to the health of mankind and to the stability of society. The coronavirus was officially named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses based on phylogenetic analysis. SARS-CoV-2 is considered to be a viral spillover of bats or coronavirus of any other animals that has gained the ability of human-to-human transmission through intermediate hosts [2,3]. SARS-CoV-2 attacks the host via angiotensin-converting enzyme 2 (ACE2) receptors widely expressed on various immune cells and tissues/organs [4]. SARS-CoV-2 infection induces an unbalanced immune response, characterized by a weak production of interferons (IFNs) and an exacerbated release of proinflammatory cytokines, and it contributes to the severe forms of the disease [5]. SARS-CoV-2 also can produce a cytokine storm, impair interferon (IFN) responses, and inhibit antigen expression on both major histocompatibility complex class I and class II [5,6]. COVID-19 symptoms range from mild types with flu-like symptoms (fever, cough, and muscle pain) to moderate types including such as pneumonia and localized inflammation that require hospitalization and severe/critical types with fatal outcomes [1,4,7]. Most (about 80%) patients with COVID-19 are asymptomatic or reveal mild/moderate symptoms. However, about

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https://doi.org/10.1016/j.jgr.2022.02.006

15% of patients have severe symptoms and approximately 5.0% of cases are severe or critical that can eventually lead to acute respiratory distress syndrome (ARDS), sepsis or septic shock (disseminated intravascular coagulation), low blood pressure, and multi-organ dysfunction/failure with other serious complications [1,4,7,8]. As of July 27, 2021, 195 million COVID-19 infections with 4.17 million deaths have been recorded (WHO; https://coronavirus.jhu.edu/map.html).

In serious cases, immunopathological events might be produce the clinical exacerbation of COVID-19. Especially, levels of pro-inflammatory cytokines are excessively elevated during the interaction between epithelial/immune cells in COVID-19. These pro-inflammatory cytokines are associated with the "cytokine storm" in those with serious complications and bad prognosis in COVID-19 [9–11]. Cytokine storm is a condition of unregulated systemic hyper-inflammation caused by an excessive production of proinflammatory cytokines that can produce multiple organ dysfunction syndromes (MOSD) and even MOSD-related mortality. MOSD is characterized by acute lung/liver/kidney failure, cardiovascular disease, and a wide spectrum of hematological abnormalities and neurological disorders [9–11]. The term of cytokine storm was first mentioned in graft-versus-host disease in 1993. It was later, reported in various pathological environments, including malignancy, rheumatologic disease, sepsis syndrome, primary and secondary hemophagocytic lymphohistiocytosis, and auto-inflammatory disorders [9–11]. Accumulating evidence suggests that cytokine storm might contribute to the mortality of COVID-19 patients [9].

Currently, various medications such as chloroquine, hydroxychloroquine, remdesivir, favipiravir, ritonavir, lopinavir, ribavirin, and dexamethasone have been introduced to control cytokine storms [12]. Most currently, Paxlovid (nirmatrelvir and ritonavir; Pfizer, US) and molnupiravir (Lagevrio, Merck, UK) have been authorized to treat mild to moderate COVID-19 (https://www.fda.gov). However, effective and specific therapeutic recommendations have not been issued for new variants of SARS-CoV-2 up to date [12]. Fortunately, in recent accumulating evidences, novel mechanism targeting cytokine storm, such as interleukin (IL)-1β and IL-6 or Janus kinase (JAK) pathway have suggested as promising potential to treat COVID-19 [13]. Additionally, it has been known that herbal extracts such as *Panax ginseng* (Korean ginseng; KG) and their bioactive compounds with immunomodulatory properties can suppress cytokine storm associated with various inflammatory and infectious diseases [8,14]. Therefore, this review will summarize cytokine storm of the COVID-19 patients and determine whether *Panax ginseng* and its pharmacologically active-ingredients (specifically, total extract, saponin, and non-saponin) might play an essential role in treating and mitigating the cytokine storm in COVID-19 patients. Experimental and clinical validation about the effectiveness of *Panax ginseng* and *Panax ginseng*-derived products to prevent or reduce cytokine storm indicate that they might be useful as adjunct treatments to control cytokine storm associated with COVID-19 infection.

2. Methods

A literature search was performed using PubMed, Scopus, and Google Scholar to find relevant articles regarding the pathogenesis of COVID-19 and cytokine storm associated with COVID-19 from January 2019 to July 27, 2021. Search terms of 'Panax ginseng', 'saponin', 'non-saponin', or 'ginsenoside' with 'COVID-19', 'SARS-CoV-2', 'cytokine storm', or 'cytokine' were used. Experimental, evidential, and clinical data with the potential to effectively control cytokine storm related to SARS-CoV-2 infection were selected, interpreted, and discussed.

3. Pathogenesis of COVID-19

The spike (S) protein of SARS-CoV-2 contains two functional subunits, S1 containing receptor binding site and S2 which is involved in membrane fusion, in addition to its N-terminal and C-terminal [3,15]. Viral infection of SARS CoV-2 is initiated by the binding of S protein to angiotensin-converting enzyme 2 (ACE2) receptor [3,15]. ACE2, a peptidase of the renin-angiotensin system, has diverse physiological functions including regulation of the renin-angiotensin system and acceleration of amino acid transporters [3,15]. The receptor-binding domain (RBD) of the S1 subunit can directly bind to the peptidase domain of ACE2 [3,15]. Cellular proteases including furin, transmembrane protease serine subtype 2 (TMPRSS2), and cathepsin L (cysteine protease) will cleave S protein at the S1/S2 and the S2' site that induces fusion of viral membrane and viral envelope with the wall of endosome, followed by the passage of nucleocapsid into the cytoplasm and the release of viral genome [15–17]. TMPRSS2 and cathepsin-L are involved in non-endosomal and endosomal viral entry pathways, respectively. Viral genomes conduced various functions such as mRNAs for translation and/or templates for genome replication and transcription. Translation occurs for the 5′-terminal two-thirds of the genome containing two open reading frames (ORFs), ORF1a and ORF1b, leading to the production of two polyproteins: pp1a and pp1ab [15–17]. Polyproteins with their two proteases (PLpro and 3CLpro) are then cleaved into 16 non-structural proteins (16 Nsps; Nsp1–Nsp16) that form RNA-dependent RNA polymerase (RdRp), a replication–transcription complex. The RdRp is responsible for replication of structural protein RNA. The remaining part of the genome following the ORF is translated into structural proteins [S, envelope (E), membrane (M), and nucleocapsids (N) proteins] in the endoplasmic reticulum. Structural proteins then move to the Golgi intermediate compartment where M protein can direct protein–protein interactions for protein assembly to form viral particles. Viral particles are transferred by exocytosis using secretory vesicles for release [15–17].

4. Immunopathogenesis and cytokine storm of COVID-19

4.1. Immunopathogenesis of COVID-19

SARS-CoV-2 infection can stimulate both innate and adaptive immune systems of the host [18,19]. The innate immune system can sense specific pathogen associated molecular patterns (PAMPs) (such as cell surface and cytosolic PAMPs) and death associated molecular patterns [18]. Adaptive immune system is mediated by the activation of T cells and the secretion of various antigen specific antibodies by B cells [19]. Activation of innate and adaptive immune systems will enhance the secretion of pro-inflammatory cytokines/chemokines [such as IL-6, IFN-γ, macrophage chemoattractant protein-1 (MCP-1), and IFN-γ-inducible protein-10 (IP-10)], further promoting the recruitment of macrophages/neutrophils into the infected areas and the blood of afflicted patients [18,19]. These immune cells can release various cytokines and chemokines to help heal the infection. Although a rapid and well-established innate and adaptive immune system is normally the first line of defense against viral infection and its elimination, excessive innate immune response and deteriorated adaptive immune response may induce destruction of host cells/tissues/organs in sites infected with the virus and all over the body [18,19]. Accumulating reports indicate that the "cytokine storm", an uncontrolled over-production of cytokines is a major responsible for the immunopathogenesis in COVID-19 patients [20] (Fig. 1).

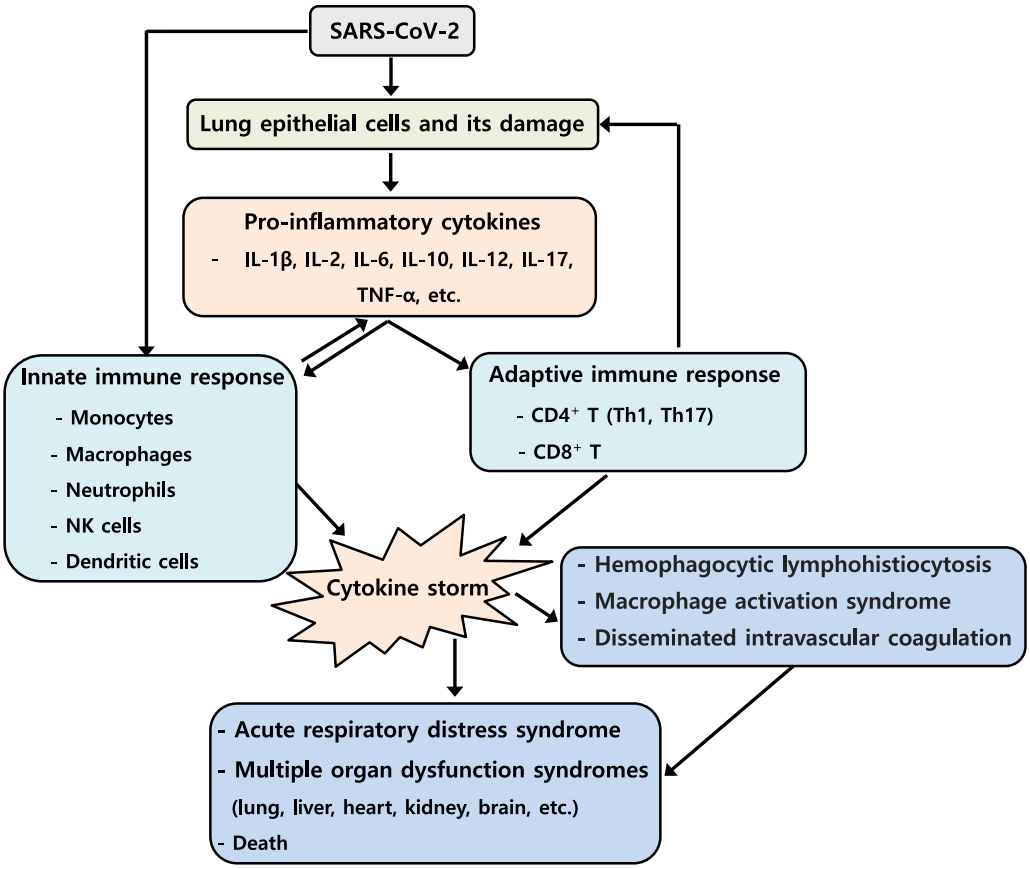

Fig. 1. *The immunopathological mechanisms of cytokine storm in COVID-19.* SARS-CoV-2 infects the respiratory epithelial cells or induces immune response, resulting in secretion of inflammatory cytokines and damage of cells and tissues. The cytokines stimulate innate immune response as well as adaptive immune response to induce the excessive production of circulating cytokines. The excessive cytokines can destroy epithelial cells or produces hemophagocytic lymphohistiocytosis, macrophage activation/acute respiratory distress syndrome and intravascular coagulation. This events together produce to acute respiratory distress syndrome, multiple organ dysfunction syndromes (lung, liver, heart, kidney, brain, etc.), or death.

4.2. Cytokine storm of COVID-19

SARS-CoV-2 infection can produce excessive inflammatory response by releasing a large amount of pro-inflammatory cytokines/chemokines in infectious tissues or organs. Remarkably, COVID-19 patients in intensive care units have extremely high levels of inflammatory cytokines such as IL-2, IL-7, IL-10, IP-10, tumor necrosis factor-alpha (TNF-α), granulocyte-colony stimulating factor (G-CSF), macrophage inhibitory protein 1-alpha (MIP1-α), and MCP-1 in plasma samples than COVID-19 patients not admitted to an intensive care unit [5]. Several studies have also reported that COVID-19 patients have extremely high levels of IL-6 in circulation and extended population of $CD14^+/CD16^+$ monocytes secreting IL-1β and IL-6 than healthy controls [9,11,21] (Fig. 1). Such explosive elevation in levels of these cytokines can result in the generation of "cytokine storm" which is primarily responsible for acute respiratory distress syndrome and MOSD in COVID-19 patients.

As above, cytokine storm of COVID-19 is a complicated and changeable immune and inflammatory response induced by a variety of cytokines from the initiating stage, leading to hyperactivation of the immune system (innate and adaptive) and MOSD [9,11]. To effectively control COVID-19, safe and precise therapeutic interventions need to be developed to control the cytokine storm associated with its infection. Controlling ongoing inflammatory events by selectively or non-selectively controlling the release of cytokines or associated signaling pathways to normalize the host immunoregulatory system is the basic therapeutic strategy for cytokine storm [6]. In this section, we will discuss the role of critical inflammatory cytokines and related mechanisms participated in cytokine storm of COVID-19.

IL-6-induced JAK/STAT signaling: IL-6, a member of the IL-6-type cytokines family, is first secreted by members [monocytes, macrophages, and dendritic cells (DCs)] of the mononuclear phagocyte system. It acts as a main stimulator of JAK family members (JAK1-3 and TYK2), inducing to the activation of transcription factors of the signal transducer and activator of transcription (STAT) family, specifically the STAT3 pathway, in the context of inflammation [22]. The IL-6/JAK/STAT3 signaling is closely associated with the severity of COVID-19 [21]. A retrospective multicenter study of 68 death cases (68/150, 45%) and 82 discharged cases (82/150, 55%) with laboratory-confirmed infection of SARS-CoV-2 has shown markedly up-regulated levels of IL-6 in severe COVID-19 patients [21].

IFN-γ-induced JAK/STAT signaling: IFN-γ, an essential modulator of immune cells, plays a predominant function in the positive immune response against bacterial/viral infections via the activation of JAK1/2 and its down cascade STAT1-IFN-γ [23]. IFN-γ closely participates in various cytokine storm-related disorders associated with infectious/noninfectious diseases through its pathological role in primary hemophagocytic lymphohistiocytosis, a syndrome of failure to target pathogens such as Epstein-Barr virus and Dengue virus owing to impaired cytotoxic T cells and NK cell activity [24]. Levels of IFN-γ was significantly elevated in severe COVID-19 patients (323 pg/mL in death cases and 209 pg/mL in survival cases

[25]. The studies indicate that IFN-γ might play a critical role in the cytokine storm of COVID-19.

IL-2-induced JAK-STAT signaling: IL-2 is mainly a pleiotropic cytokine produced by activated $CD4^+$ and $CD8^+$ T cells. It plays important roles in immunological events including the proliferation/differentiation of $CD4^+$ T, $CD8^+$ T, NK, and other cells via the JAK–STAT5 pathway [6,26]. And deficiency of IL-2 is participated in the onset of autoimmune disorders such as multiple sclerosis and rheumatoid arthritis [27].

Levels of IL-2 or IL-2R in severe COVID-19 patients were enhanced [6,8]. Surprisingly, a clinical trial including 54 patients with COVID-19 has reported a contradictory result [6,8]. Inhibition of IL-2/IL-2R can lead to $CD8^+$ T cell- and lymphocyte-related decrease through JAK1-STAT5 in critical patients with COVID-19 pneumonia [6,8]. Since reports on the role of IL-2 in cytokine storm after COVID-19 are still limited, further studies are needed using samples from additional patients.

TNF-α-induced NF-κB signaling: TNF-α is secreted by macrophages/monocytes during many infectious/inflammatory/autoimmune diseases. It is responsible for signaling events within immune cells, leading to necrosis or apoptosis. TNF-α can induce nuclear factor kappa B (NF-κB) phosphorylation and trigger the expression of several pro-inflammatory and antiapoptotic genes through TNF receptor-1 and a series of intermediate adapters [28]. NF-κB can induce TNF-α expression in the status of inflammation caused by pathogen infections such as viral/bacterial infections [28]. Thus, TNF-α/NF-κB pathway may play critical pathological roles in the onset stage of inflammatory response and the excessive activation of various immune cells in cytokine storm of COVID-19 [29].

TNF-α is excessively secreted in SARS-CoV-infected monocyte-derived human DCs and human primary T cells as well as in immune cells of MERS-CoV infected humans [5]. NF-κB is activated in SARS-CoV-infected mice, while inhibition of NF-κB-mediated inflammation increases the survival of mice [29,30]. Several studies have reported that serum level of TNF-α is excessively elevated in severe COVID-19 cases [6], which is negatively correlated with the dramatic reduction of T cell numbers and the survival of COVID-19 patients [31]. On the other hand, a study has reported that a serum levels of TNF-α were within normal values in almost all COVID-19 patients [32]. Although the role of TNF-α/NF-κB signaling in COVID-19 remains controversial, control of the TNF-α–NF-κB pathway may exert beneficial effects in COVID-19 patients [6,29].

IL-10 signaling: IL-10, a human cytokine synthesis inhibitory factor, can be released by virtually all immune cells such as macrophages, DCs, T helper-2 (Th2), Tregs, $CD8^+$ T cells, and NK cells. IL-10 signals through the IL-10R/JAK/STAT3 pathway via activation of cytoplasmic tails of IL-10R1/IL-10R2 [33]. IL-10 plays anti-inflammatory roles by directly controlling the innate immune response of macrophages and DCs in an autocrine/paracrine manner or by indirectly improving Treg development. IL-10 can also activate mast cell-mediated immune responses and strengthen roles of $CD8^+$ T, B, and NK cells [34].

Recently, a clinical trial enrolling 102 COVID-19 patients and 45 controls has reported that serum levels of IL-10 are higher in patients with a critical illness than in patients with moderate or severe COVID-19. The higher concentrations of IL-10 are positively related with levels of serum C-reactive protein [35]. Since IL-10 has a potent immunomodulatory or anti-inflammatory effect [34], adequate releases of IL-10 in patients with COVID-19 may control inflammation by downregulating the hyperactivity of the immune system. Since IL-10 is clearly a gatekeeper of fibrotic/antifibrotic signaling to reduce fibrosis [36], IL-10 may improve acute respiratory distress syndrome [37] or its milder form acute lung injury. Thus, controlling activity, production, or secretion of IL-10 with appropriate protocols such as the use of a neutralizing antibody and an antagonist of IL-1 in the early phage of SARS-CoV-2 infection may be an attractive therapeutic intervention.

IL-12 signaling: IL-12 (IL-12p70) is an important immunoregulatory cytokine that is naturally released by neutrophils, B cells, and antigen-presenting cells in response to antigenic stimulation [38]. IL-12 is also produced by immune cells to defend against infections such as an influenza virus infection, and it can induce IFN-γ secretion and trigger $CD4^+$ T cells to differentiate into type 1 T helper (Th1) cells during infection [5]. IL-12 can also augment the cytotoxicity of NK cells [38]. IL-12 can stimulate the production of IFN-γ from Th1 and NK cells, thus preventing viral replication. Levels of IL-12 are increased in plasma samples of SARS-CoV infected patients [5,6]. These reports suggest that IL-12 may play a positive function in cytokine storm by magnifying the activity of various immune cells.

IL-17A signaling: IL-17A, the most widely studied member of the IL-17 cytokine family, is produced by Th17, $CD8^+$ T, and type 3 innate lymphoid cells. IL-17A can mediate many pro-inflammatory/allergic responses and autoimmune diseases and play various roles in tissue/organ damage, physiological stress, and infection [37]. IL-17 can interact with IL-22 (mainly produced by T helper 22 cells in humans, but by T helper 17 cells in mice) to induce expression of antimicrobial peptides in keratinocytes [5,37]. Although targeting IL-17A is now considered as an attractive approach to treat several autoimmune and infectious diseases [39], roles of IL-17A remain largely unknown.

Level of IL-17 is enhanced in the fluid of bronchoalveolar lavage of acute lung injury model in animal. Enhancement of IL-17 can increase severity of acute lung damage, however, inhibition of IL-17 can inhibit and alleviate it [40]. Levels of IL-17 are elevated in COVID-19 patients, especially in those with a severe and critical illness [41]. IL-17 is important in the process of hyperactivation of various immune cells and MOSD of COVID-19 patients by inducing the recruitment/infiltration of immune cells including neutrophils and expressing pathological events such as tissue damage and recovery [42]. Interestingly, anti-IL-17 therapy (netakimab) can mitigate the inflammatory response and improve oxygenation of hospitalized patients with severe COVID-19 [43]. These results indicate that agents that can regulate the production and secretion of IL-17A might have intervention potential by targeting cytokine storm associated with COVID-19.

5. Panax ginseng as an adjuvant treatment for immunopathogenesis and cytokine storm of COVID-19

Panax ginseng, a famous traditional herbal medicine, have long been known to play an important role in preventing/treating various abnormal conditions. They have a holistic concept of strengthening body resistance to microbial infection [44–48]. The significance of *Panax ginseng*, a representative Oriental traditional medicine, in the management of infectious diseases and various inflammatory disorders has been proven. Early administration of *Panax ginseng* can improve the recovery rate and reduce the mortality rate in viral infected patients and animal models [47,48]. Recently, *Panax ginseng* has been suggested as a beneficial supplement in the management of COVID-19 pandemic [48]. Various studies have clearly specified that *Panax ginseng* not only can prevent virus replication, but also can dampen the inflammatory storm by controlling immune responses [44–46]. Moreover, its main active components have immunomodulatory properties by upregulating expression levels of anti-inflammatory cytokines and down-regulating the expression of proinflammatory cytokines [49,50]. In this section, we will review studies some in vitro/vivo and clinical trials showing that *Panax ginseng* exhibit both anti-inflammatory and tissue-protecting activities with an idea of

employing *Panax ginseng* as a mode of phytotherapy for treating COVID-19.

5.1. Total extract

Panax ginseng extract consists of saponin (ginsenosides) and non-saponin (polysaccharides, peptides, polyacetylenic alcohols, and fatty acids) fractions. It can inhibit the production of various proinflammatory cytokines and elevate the production of anti-inflammatory cytokines in various in vitro/vivo studies [44–46]. For example, Korean Red Ginseng (KRG) extract (KRGE) can increase protein expression levels of aging-related genes such as Lin28a, growth differentiation factor-11, Sirt1, IL-2, and IL-17 in thymocytes of old murine and the population of Treg cells and IFN-γ-expressing NK cells in the spleen, suggesting that KRGE has anti-aging effects by modulating the expression of aging-related genes and immune cell subsets [51]. KRGE exhibits an antiviral activity by inhibiting viral replication associated with suppressed expression of IL-6 and TNF-α genes in respiratory syncytial virus-induced human epithelial cells and the expression of IL-8 in murine dendritic and macrophage-like cells as well as enhanced levels of IFN-γ in DCs [52,53]. KRGE can improve lung viral clearance and enhance the production of IFN-γ in bronchoalveolar lavage cells and increase populations of $CD8^+$ T cells and $CD11c^+$ DCs in bronchoalveolar lavage fluids from respiratory syncytial virus-infected mice [52].

5.2. Saponins

Ginseng saponins (ginsenosides), a class of steroid glycosides and triterpene saponins in natural products, are the major active ingredients found in KR and KRG [54]. Ginseng ginsenosides and their metabolites/derivatives—including ginsenoside-Rb1, -Rb2, -Rd, -Re, -Rg1, -Rg2, -Rg3, -Rg5, -Rh1, -Rh2, -Rp1, and compound K [55,56]—are responsible for various biological/pharmacological activities (such as immunomodulatory, neuroprotective, cardioprotective, and anti-inflammation/-oxidation/-cancer actions) of ginseng by regulating signaling pathways such as NF-κB and JAK/STAT in cell culture or animal models, although their relevance to human biology is unknown [44,55,57–59].

As summarized in the Table 1, total ginseng saponin has certain benefits, including decreasing the toxicity levels in the liver, reducing oxidative stress, diminishing pro-inflammatory factors, and augmenting the levels of glutathione and superoxide dismutase in the cyclophosphamide-induced liver injuries in rats [60]. Ginsenoside-Rb1 can mitigate osteoarthritis by reducing serum levels of several proinflammatory cytokines (IL-1β, IL-6, and IFN-γ) and chemokines (CCL-2 and MCP-1) in monoiodoacetate-induced osteoarthritis of ovariectomized rats as a model of post-menopausal arthritis [61]. Ginsenoside-Rb1 exhibits anti-cachexia activity by improving gastrocnemius muscle weight or epididymal fat weight in cancer (C26 cells)-induced cachexia model of mice [62] through down-regulation of protein or serum levels of IL-1β, IL-6, and IFN-γ. Ginsenoside-Rb1 can also reduce lung histological injury and levels of IL-6, TNF-α, and malondialdehyde as well as wet/dry weight ratio related to increased expression of nuclear factor erythroid 2–related factor 2 (Nrf2) and heme oxygenase (HO)-1 in lung tissues from mice with intestinal ischemia reperfusion injuries [63]. Ginsenoside-Rg3 can reduce gene expressions of cytokines (IL-4, IL-5, IL-6, IL-13, and TNF-α) and chemokines (CCL11 and CCL24), promote HO-1 expression, and increase Nrf2 secretion in lung tissues of an asthma murine model sensitized with ovalbumin [64]. Ginsenoside-Rg3 can mitigate pathological damages, reduce myeloperoxidase activity, decrease the secretion of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α, and reduce polarization of M1 macrophages. Furthermore, it can promote the production of anti-inflammatory mediators IL-10 and TGF-β and enhance polarization of M2 macrophages via Mer receptor tyrosine kinase-dependent up-regulation of the PI3K/AKT/mTOR pathway [65]. Ginsenoside-Rg3 can inhibit the secretion level of IL-12 from DCs and subsequent Th1 cell differentiation. It can also suppress the expression of IFN-γ and T-bet in T cells under Th1-skewing condition and the frequency of Th1 cells in the Peyer's patch and lamina propria cells *in vivo*, suggesting that ginsenoside-Rg3 has a potential to treat Th1-related diseases [66]. Ginsenoside-Rg6 can negatively regulate or downregulate pro-inflammatory cytokines IL-1β, IL-6, IL-12p40, and TNF-α but increase levels of pro-inflammatory cytokine IL-10 related to the reduction of mitogen-activated protein kinases (MAPKs) and NF-κB activations in the sera of septic mice or lipopolysaccharide (LPS)-activated bone-marrow-derived macrophages through induction of IL-10 and miR-146a [67]. A combination of ginsenoside-Rg2 and -Rh1 exhibits anti-inflammatory activity by downregulating mRNA levels of pro-inflammatory cytokines (IL-1β, IFN-β, and TNF-α) and blocking p38 MAPK activation and NF-κB translocation by inhibiting the binding of LPS to toll-like receptor 4 (TLR4) on peritoneal macrophages [67–69]. Ginsenoside-Rh1 can reverse the increase of pro-inflammatory cytokines (IL-4, IL-5, IL-13, and IL-33) and eotaxin (a potent chemoattractant for eosinophils) and the decrease of IL-12 and IFN-γ in both BALF and serum samples of ovalbumin-sensitized asthma model of mice [68] (Table 2). Ginsenoside-Rk1 shows anti-inflammatory effect by inhibiting the expression of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α), NO, and monocyte chemotactic protein (MCP)-1 and by blocking the activation of NF-κB and JAK2/STAT3 pathways in LPS-stimulated RAW264.7 cells [70]. Ginsenoside-Rk3 can repair intestinal barrier dysfunction by enhancing the expression of tight junction proteins (zonula occludens-1, occluding, and claudin-1) associated with the reduction of colonic inflammatory cytokine levels (IL-1β, IL-6, and TNF-α) in an antibiotic-mediated gut microbiota disturbance model [71]. Diol-ginsenosides can decrease IL-1β and TNF-α production in RAW246.7 cells after LPS or IFN-γ stimulation [72] (Table 1). In conclusion, total saponin and various types of ginsenosides might be used in medicinal interventions to control the cytokine storm associated with COVID-19 by preventing the secretion of proinflammatory cytokines and enhancing the production of anti-inflammatory cytokines via regulation of MAPKs, NF-κB, JAK/STAT, and Nrf2 signal pathways.

5.3. Non-saponin

Non-saponin components of KG or KRG can be classified into saccharides (mono-/di-/tri-/poly-saccharides, crude fiber, and pectin), nitrogen-containing compounds (amino acid, peptide, protein, nucleic acids, and alkaloid), fat-soluble components (lipid, fatty acid, polyacetylenes, phenolic compounds, essential oils, phytosterols, organic acid, and terpenoid), water-soluble vitamins, and minerals [73]. Recently, accumulating evidences have demonstrated that non-saponin and it ingredients have attractive physiological features (such as adaptogen), immunoregulatory effects, and pharmacological features (such as anti-inflammatory/-oxidant and neuroprotective effects [73]. In this section, we will discuss the potential effect of non-saponin on cytokine storm of COVID-19 patients.

Non-saponin: The non-saponin fraction of KRG can decrease glucose uptake and transport in vitro and modulate glucose production related to the reduction of proinflammatory cytokines (IL-1β and TNF-α) in blood via down-regulation of the PI3K/AKT pathway *in vivo* [74]. The non-saponin fraction can also attenuate the production of cytokines (IL-1β, IL-6, IL-10, and TNF-α) via

Table 1
Ginseng saponin as potential therapeutic agents for mitigating and managing cytokine storms of COVID-19.

Compounds	Inflammatory Modulators	Effects and Signal Pathway	Assay Models	References
Total saponins	↓ Cytokines (IL-1β and TNF-α); ↓ Hepatic toxicity (ALT, ALB, ALP, and AST); ↓ Oxidative stress (MDA, NO); ↑ Enzymes (GSH and SOD)	Anti-toxicity in liver (cytochrome P450; l-arginine/NO pathway)	Cyclophosphamide-induced liver injuries in rats	[60]
Ginsenoside-Rb1	↓ Cytokines (IL-1β, IL-6, and IFN-γ) and chemokines (CCL-2 and MCP-1)	Anti-inflammatory	Serum of monoiodoacetate-induced osteoarthritis of ovariectomized rats	[61]
	↓ Cytokines (IL-6, and TNF-α)	Anticachexia	Cancer-induced cachexia model in mice	[62]
	↓ Cytokines (IL-6, TNF-α) and MDA; ↑ SOD and IL-10 in the lung tissues	Antioxidative (Nrf2/HO-1)	Intestinal ischemia-reperfusion injury model in mice	[63]
Ginsenoside-Rg3	↓ Cytokines (IL-4, IL-5, IL-6 IL-13, and TNF-α) and chemokines (CCL11 and CCL24)	Antioxidative (Nrf2/HO-1)	Lung of ovalbumin-sensitized asthma murine model	[64]
	↓ Cytokines (IL-1β, IL-6, and TNF-α); ↑cytokines (IL-10 and TGF-β)	MerTK-dependent activation of the PI3K/AKT/mTOR pathway	LPS-induced acute lung injury in mice	[65]
	↓ Cytokine (IL-12) from DCs; ↓ Th1 cell differentiation; ↓ IFN-γ and T-bet in T cells under Th1-skewing condition	Cell differentiation	Th1 cell; Peyer's patch and lamina propria cells; Rg3-treated mice	[66].
	↓ Cytokines (IL-1β, IL-6, IL12p40, and TNF-α) and neutrophil infiltration; ↑ cytokine (IL-10)	Immunosuppressive	LPS-induced septic mice or BMDMs	[67]
Ginsenoside-Rh1	↑ Cytokines (IL-4, IL-5, IL-13, and IL-33) and eotaxin; ↓ Cytokines (IL-12 and IFN-γ)	Anti-inflammatory; Th1/Th2 cytokines balance	OVA-sensitized asthma model in mice	[68]
Ginsenoside-Rg2/-Rh1 combination	↓ Cytokines (IL-1β, IFN-β, and TNF-α)	Anti-inflammatory (p38 MAPK and NF-κB)	LPS-stimulated peritoneal macrophages	[69]
Ginsenoside-Rk1	↓ Cytokines (IL-1β, IL-6, TNF-α), NO, and monocyte chemotactic protein (MCP)-1	Anti-inflammatory (NF-κB and JAK2/STAT3	LPS-stimulated RAW264.7 cells	[70]
Ginsenoside-Rk3	↓ Cytokines (IL-1β, IL-6, and TNF-α); ↓ Tight junction proteins (ZO-1, occluding, and claudin-1)	Anti-inflammatory	Antibiotic-mediated gut microbiota disturbance model	[71]
Diol-ginsenosides	↓ Cytokines (IL-1β and TNF-α) and NO		LPS or IFN-γ stimulated RAW246.7 macrophages	[72]

Abbreviations: ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMDMs, bone-marrow-derived macrophage; GSH, glutathione; HO-1, heme oxygenase-1; IFN-γ, interferon-gamma; IgG, immunoglobulin G; IL, interleukin; JAK2, Janus kinase 2; LPS, lipopolysaccharide; MAPKs, mitogen-activated protein kinases; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde; MerTK, MER proto-oncogene, tyrosine kinase; NF-κB, nuclear factor κB; NO, nitric oxide; Nrf2, nuclear factor erythroid-2-related factor 2; OVA, ovalbumin; PI3K, phosphatidylinositol 3-kinase; SOD, superoxide dismutase; STAT3, signal transducer and activator of transcription 3; TGF-β, transforming growth factor-beta; Th, helper T cells; TNF-α, tumor necrosis factor-alpha; ZO-1, zonula occludens-1.

inhibition of TLR4-MyD88-NFκB pathway in peritoneal macrophages of lysophosphatidic acid (LPA) or alum-induced peritonitis in mice, indicating that non-saponin may inhibit TLR4 expression in immune cells such as macrophages, thereby reducing the secretion of cytokines during peritonitis [75] (Tale 2).

Polysaccharides: Ginseng polysaccharides have preventive effects on influenza infection. They can moderately enhance the survival rate and lower viral titers and levels of cytokine IL-6 in lungs of H1N1 (A/PR/8/34)- and H3N2 (A/Philippines/82) influenza viruses-infected mice [76]. Interestingly, a comparative study about effects of whole KRGE, saponin, and polysaccharide fractions on influenza A (H1N1) virus infection has shown that the polysaccharide fraction can increase the survival rate (80%) than the total extract or saponin fraction (survival rate of 67% or 56%, respectively) [77]. Moreover, the polysaccharide fraction is the most effective one in reducing the accumulation of TNF-α/inducible NO synthase [1]-producing DCs in mouse lungs [77] (Table 2).

As summarized in the Table 2, ginseng berry polysaccharide has beneficial effects on the activation of NK cells and the inhibition of tumors by inducing the greatest upregulation of IL-6, IL-12, and TNF-α and by inducing the release of IFN-γ and granzyme B by NK cells [78]. Polysaccharides isolated from leaves of *Panax ginseng* can lead to higher levels of ovalbumin-specific Th1-type (IL-2, IFN-γ, GM-CSF) and Th2-type (IL-10) cytokines in the culture supernatant isolated from splenocytes of ovalbumin-immunized asthma model of mice. The polysaccharides can lead to T cell proliferation and reduce the production of IgE antibody in an in vitro assay [79]. Dietary supplementation with ginseng polysaccharides can increase concentrations of total immunoglobulin G, IL-2, IL-6, TNF-α, and IFN-γ in serum/milk of sows as well as IL-2 and TNF-α concentrations in the sera of piglets of experimental groups, indicating the potential of using ginseng polysaccharides to improve immunity-related bio-marker levels in sow serum/milk [80]. These positive effects might further improve the health and growth of piglets through biological transmission effects [80] (Table 2).

Acidic polysaccharide: Acidic polysaccharide from *Panax ginseng* can suppress an encephalitogenic response during experimental autoimmune encephalomyelitis (EAE), an animal model of MS, by preventing the proliferation of autoreactive T cells and the expression of inflammatory cytokines such as IFN-γ, IL-1β, and IL-17 [81]. Furthermore, acidic polysaccharide can enhance the population of immunosuppressive Treg cells via the activation of Foxp3 [81]. Acidic polysaccharide can induce Th1 cell and macrophage cytokines (IL-1α, IL-2, IFN-γ, and GM-CSF) and the generation of lymphokine-activated killer cells (LAK cells; cytolytic lymphocytes with the unique capacity of killing NK-resistant fresh human tumor cells in short-term assays) in synergy with recombinant IL-2 [82]. These results suggest that acidic polysaccharide may lead to the generation of LAK cells from both NK and T cells by inducing endogenous production of multiple cytokines and that acidic polysaccharide might have positive efficacy in immunoprevention and immunotherapy of cancer [82]. Acidic polysaccharide can also induce cytotoxic activity against B16 melanoma cells by increasing levels of cytokines including IL-1β, IL-6, IFN-γ, and TNF-α and enhancing the production of reactive oxygen and nitrogen species such as nitric oxide and hydrogen peroxide [1] (Table 2).

p-coumaric acid: p-coumaric acid, an active ingredient of *Panax ginseng,* can suppress mRNA expression levels of IL-1β, IL-6, TNF-α, and thymic stromal lymphopoietin (TSLP) in a human mast cell line-1 and decrease mRNA/protein expression levels of IL-4, IL-6, and TSLP in atopic dermatitis-like skin lesions associated with downregulated expression of RIP2, caspase-1, p-p38/p-*c*-Jun N-terminal kinase (JNK)/p-extracellular signal-regulated kinase (ERK), and *p*-IKKβ/p-IkBα/NF-κB [83].

Table 2
Ginseng non-saponin as potential therapeutic agents for mitigating and managing cytokine storms of COVID-19.

Compounds	Inflammatory Modulators	Effects and Signal Pathway	Assay Models	References
Red ginseng marc oil	↓ Cytokines (IL-1β, IL-6, and TNF-α); ↓ PGE2	Anti-inflammatory (p38 MAPK/NF-κB)	LPS-stimulated RAW 264.7 macrophages	[73]
Total non-saponin	↓ Cytokines (IL-1β and TNF-α) in blood	Anti-inflammatory (PI3K/AKT)	C57BLKS/J$^{db/db}$ (diabetic) mice	[74]
	↓ Cytokines (IL-1β, IL-6, IL-10, or TNF-α) in peritoneal macrophages	Anti-inflammatory (TLR4-MyD88-NFκB)	LPA or alum-induced peritonitis in mice	[75]
Polysaccharide (from the ginseng)	↓ Cytokine (IL-6) and viral titer in lung; ↑ survival rate	Preventive effect on influenza infection	H1N1 (A/PR/8/34) and H3N2 (A/Philippines/82) influenza viruses-infected mice	[76]
	↓ Cytokine (TNF-α) and iNOS-producing DCs in the lungs; ↑ survival ratio (80%)	Antiviral; Anti-inflammatory	Influenza A virus-infected mice	[77]
	↑ Cytokines (IL-2, IL-6, TNF-α, and IFN-γ) and total IgG in milk/serum	Immune boost	Sows and its piglets	[80]
Polysaccharides (from the leaves)	↑ Cytokines [(Th1-type; IL-2, IFN-γ, GM-CSF) and (Th2-type; IL-10)]	Immunoadjuvant activity	OVA-immunized asthma model in mice	[79]
Polysaccharide (from the berry)	↑ Cytokines (IL-1β and TNF-α); ↑ NK cell cytotoxicity	Immunostimulating; Antimetastatic; Anti-cancer	Murine peritoneal macrophages; YAC-1 tumor cells; B16BL6 melanoma cells	[78]
Acid polysaccharide	↓ Cytokines (IFN-γ, IL-1β and IL-17); ↑ Activation of Treg cell	Immunemodulating (Treg cells)	MOG_{35-55}-induced EAE in mice for MS	[81]
	↑ Cytokines (IL-1α, IL-2, IFN- γ, and GM-CSF) in Th1 and macrophages; ↑ Lymphokine-activated killer cells	Immunopreventive; Immunotherapy	Th1 cell; Macrophages; Lymphokine-activated killer cells	[82]
p-coumaric acid	↓ Cytokines (IL-1β, IL-6, or TNF-α) and thymic stromal lymphopoietin	Anti-inflammatory (↓ MAPKs/NF-κB)	Human mast cell line-1; 2,4-dinitrofluorobenzene-induced atopic dermatitis	[83]
Gintonin	↓ Cytokines (IL-1β, IL-6, TNF-α), chemokines (MCP-1, MIP-1α, and RANTES), and enzymes (COX-2 and iNOS); ↓ The percentages of Th1 and Th17 cells; ↑ The percentages of Treg cells; ↓ IFN-γ, IL-17, and TGF-β	Anti-inflammatory (MAPKs/NF-κB); Antioxidative (Nrf2); Neuroprotective; Activation of LPA receptors	MOG_{35-55}-induced EAE model in mice for MS	[86]
	↓ Cytokines (IL-1β, IL-6, TNF-α), and enzymes (COX-2 and iNOS)		3-NPA-intoxicated striatal toxicity model in mice for HD; STHdh cells; AAV-82Q vector-induced HD models in mice	[87]
	↓ Cytokine (IL-6 and TNF-α) and enzyme (COX-2)		MPTP-induced model in mice for PD	[88]
Gintonin-enriched fraction	↓ Cytokine (IL-6); Cytokine (IL-18); ↓ GR; ↓ NLRP3 inflammasome	Anti-inflammatory; Anti-oxidative; LPA receptor	Heat stress-induced C2C12 cells	[89]

Abbreviations: COX-2, cyclooxygenase-2; DCs, dendritic cells; GM-CSF, granulocyte-macrophage colony-stimulating factor; GR, glutathione reductase; IFN-γ, interferon-gamma; IgG, immunoglobulin G; IL, interleukin; iNOS, inducible nitric oxide synthase; LPA, lysophosphatidic acid; MAPKs, mitogen-activated protein kinases; MCP-1, monocyte chemoattractant protein-1; MIP-1α, macrophage inflammatory protein-1α; NF-κB, nuclear factor κB; NK, natural killer; NLRP3, NOD-like receptor pyrin domain-containning protein 3; NO, nitric oxide; Nrf2, nuclear factor erythroid-2-related factor 2; PGE2, prostaglandin E2; PI3K, phosphatidylinositol 3-kinase; RANTES, regulated on activation, normal T cell expressed and secreted; TGF-β, transforming growth factor-beta; Th, helper T cells; TLR4, toll like receptor; TNF-α, tumor necrosis factor-alpha; Treg, regulatory T.

Gintonin: Gintonin, an active non-saponin of *Panax* ginseng, is a glycolipoprotein complex that contains three lipid-derived G protein-coupled receptor (GPCR) ligands: LPAs, lysophosphatidylinositols, and linoleic acid. These three GPCR ligands act on six LPA receptor (LPAR) subtypes, G protein-coupled receptor (GPR) 55, and GPR40, respectively [84]. Recently, gintonin's bioactivities have been clarified [85,86]. Gintonin can inhibit the expression of IL-6, TNF-α, iNOS, and COX-2. It is associated with prevention of NF-κB/p65 from moving into the nucleus through JNK and ERK MAPKs phosphorylation in fibroblast-like synoviocytes [85]. Gintonin can exert neuroprotective effects in EAE. It can alleviate motor disability of EAE mice related to decreased demyelination, reduced infiltration/activation of immune cells, and diminished expression of inflammatory chemokines (MCP-1, MIP-1α, and RANTES), cytokines (IL-1β, IL-6, and TNF-α), and enzymes (COX-2 and iNOS) in the spinal cord. Gintonin can reduce percentages of Th1 and Th17 cells but increase the percentages of Treg cells in the spinal cord, in agreement with changed mRNA expression of IFN-γ, IL-17, and TGF-β in the spinal cord. The underlying mechanism is associated with the down-regulation of ERK and p38 MAPKs and NF-κB pathways and the activation of Nrf2 via increased expression of LPAR1-3 [86] (Table 2). Gitonin has neuroprotective effects on several neurodegenerative diseases [87,88]. For instance, pretreatment with gintonin can alleviate the severity of motor disability and lethality after treatment with 3-nitropropionic acid. Such effect of gintonin is associated with attenuated mitochondrial dysfunction, apoptosis, microglial activation, and mRNA expression of inflammatory mediators (IL-1β, IL-6, TNF-α, COX-2, and iNOS) in the striatum. Its underlying mechanisms have been confirmed as upregulation of Nrf2 pathway and down-regulation of MAPKs and NF-κB pathways through down-regulation of LPARs [87]. Gintonin can also ameliorate motor disability and the enhanced survival rate associated with the inhibition of loss of tyrosine hydroxylase–positive neurons, microglial activation, activation of inflammatory mediators (IL-6, TNF-α, and COX-2), and alteration of BBB integrity by the activation of the Nrf2/HO-1 pathways and the inhibition of phosphorylation of MAPK and NF-κB pathways via LPARs [88] (Table 2). Gintonin-enriched fraction can inhibit the secretion of inflammatory cytokines such as IL-6 and IL-18 and decrease the expression of glutathione reductase and catalase related to oxidative stress. Such effect is also related to the reduction of p-p38, *p*-ERK, and NLRP3 inflammasome through lysophosphatidic acid (LPA) receptor in heat stress-induced C2C12 cells (an immortalized mouse myoblast cell line), suggesting the potential of using gintonin-enriched fraction to protect muscle cells from heat stress and inhibit tissue/organ injury caused by oxidative stress and inflammation [89] (Table 2). Taken together, total non-saponin and its ingredients including polysaccharides, *p*-coumaric acid, and gintonin have positive activities on various physiological and pathological conditions related to the reduction of proinflammatory cytokines and

the induction of anti-inflammatory cytokines through the activation or inhibition of MAPKs, NF-κB, Nrf2, and LPARs. Thus, ginseng non-saponin might have a potential to control cytokine storm in COVID-19.

5.4. Modified types based on Panax ginseng and its ingredients

Nanoencapsulation: Nanoencapsulation-based technologies are unique and novel in the food and pharmaceutical industry with benefits such as high bioavailability, high shelf-stability, and controlled release of bioactive compounds [90]. Although ginsenoside-Rb1, the most abundant active component of ginseng, shows clinical effects as an anti-neoplastic/-oxidative/-rheumatic agent, its oral bioavailability is poor due to its low solubility [91]. One study has reported that nano-encapsulated ginsenoside-Rb1 with a high solubility has excellent anti-gouty-arthritic and anti-inflammatory effects by blocking the expression of proinflammatory cytokines (IL-1β, IL-6, and TNF-α) and agents (iNOS, glutathione peroxidase, malondialdehyde, and superoxide dismutase) by blocking protein expression of IkB -alpha, NF-κB, and NLRP3 against monosodium urate-induced gouty arthritis in rats [91] (Table 3). The results indicate that micro-/nano-sized delivery systems may increase the bioavailability of ginseng extract and ginseng-derived materials, which may help design better delivery systems to maximize the versatile therapeutic potential of ginseng-based materials to treat cytokine storm in COVID-19.

Fermentation: Fermentation is an ideal process of biochemical alteration using microbial enzymes and microorganisms. Fermentation is conducted to improve storage period, nutrition, and sensory characteristics related to foods [90]. *Panax* ginseng has many biologic therapeutic effects, including anti-inflammatory properties. Ginsenosides are considered as ingredients responsible for these therapeutic effects. However, orally treated ginseng has low bioavailability/absorption in the gastrointestinal tract (GIT) [92]. Thus, fermented ginseng has been developed to upregulate beneficial activities of *Panax ginseng* in the GIT. In this section, we will discuss potentials for the beneficial effects of *Panax ginseng* and ginseng-derived materials fermented by probiotic bacteria against cytokine storm (Table 3). Fermented KRG (F-KRG) can ameliorate IgE and IL-4 levels more, leading to Th2-type cytokine response in bronchoalveolar lavage fluid, nasal fluid, and serum samples of mice with ovalbumin-induced allergic rhinitis than KRG, suggesting that F-KRG has better immune regulatory effects than KRG. F-KRG can also downregulate levels of immune cells such as eosinophils and basophils and decrease the thickness of ovalbumin-induced respiratory epithelium compared to KRG. Collectively, these results suggest that FRG treatment can alleviate inflammation, thereby extending a protective effect to mice with ovalbumin-induced inflammatory allergic rhinitis [93] (Table 3).

Supplementation with F-KG can reduce increases of alanine transferase, aspartate transaminase, and pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) in sera of LPS-induced inflammation model of mice. Such effects are associated with the down-regulation of TLR4, caspase3, p-p38 MAPK, and *p*-ERK MAPK in the liver. Meanwhile, F-KG supplementation can increase the expression of claudin 1, an intestinal tight junction protein, in the same model. These results indicate that F-KG may alleviate LPS-induced inflammation through the TLR4/MAPK pathway and increase intestinal barrier function in mice [94] (Table 3). In conclusion, the use of modified types (nanoencapsulated and fermented) based on *Panax ginseng* and its ingredients may be a new approach to control cytokine storm in COVID-19.

5.5. Efficacy of Panax ginseng in clinical trials

Healthy adults: A clinical trial including a total of 100 healthy adult subjects has reported that KRG has immune-boosting benefits for healthy persons. Compared to the placebo group, the KRG intake group shows significantly increased numbers of T cells (CD3) and its subtypes (CD4 and CD8), B cells, and WBC count before/after 8 weeks of the intake [95]. To measure whether KRG intake could influence exercise (uphill treadmill running)-induced muscle injury and inflammation events, a clinical trial including eighteen male college students has been performed. *Panax ginseng* extract-treated group shows reduced levels of plasma creatine kinase, glucose, insulin, and IL-6 after exercise or during the recovery period. These results suggest that KRG supplementation could block exercise-related muscle injury and inflammatory responses, leading to improvements in insulin sensitivity [96]. To investigate the effect of ginsenoside-Rg1 on TNF-α and IL-10 gene expression in human skeletal muscles after exercise challenge and its effect on ergogenic outcomes, a randomized double-blind placebo-controlled crossover trial has been performed, showing that Rg1 can suppress exercise-induced increases of thiobarbituric acids reactive substance and reverse the increase of TNF-α and the decrease of IL-10 mRNA in quadriceps muscles against exercise challenge [97] (Table 4).

Patients: A clinical trial including a total of 96 non-small cell lung cancer (NSCLC) cases has shown that ginseng polysaccharides can increase levels of Th1 cytokines (IL-2 and INF-γ) and the ratio of Th1/Th2 cytokines (INF-γ/IL-4, and IL-2/IL-5), but decrease Th2 cytokines (IL-4 and IL-5) and functional assessment of cancer therapy-lung scores, suggesting a greater effect of ginseng polysaccharides on NSCLC patients' immune function [98] (Table 4). A clinical trial including 60 cases with allergic rhinitis has revealed that the KRG group shows clear improvement in rhinorrhea, nasal itching, and eye itching. Both antihistamine and KRG groups show significant decreases of total IgE, IL-4, and eosinophil counts in serum or nasal smears. Thus, KRG might be a useful treatment modality for patients with allergic rhinitis [99] (Table 4). Collectively, these findings indicate that ginseng and ginseng-derived

Table 3
Modified types based on *Panax ginseng* and its ingredients as potential therapeutic agents for mitigating and managing cytokine storms of COVID-19.

4-Materials	Inflammatory Modulators	Effects and Signal Pathway	Assay Models	References
Nano-encapsulated ginsenoside-Rb1	↓ Cytokines (IL-1β, IL-6, and TNF-α) and agents (iNOS, GPx, MDA, and SOD)	Anti-gouty-arthritic; Anti-inflammatory (↓NF-kB and NLRP3)	Monosodium urate-induced gouty arthritis in rats	[91]
Fermented ginseng	↓ Cytokines (IL-1β, IL-6, and TNF-α); ↓ TLR4, caspase3, p-p38 MAPK, and *p*-ERK MAPK; ↓ Claudin 1	Anti-inflammatory; TLR4/MAPK	LPS-induced inflammation model in mice	[94]
Fermented red ginseng	↓ IgE and cytokine (IL-4); ↓ Activation of eosinophils and basophils	Anti-inflammatory; Anti-allergic	OVA-induced allergic rhinitis in mice	[93]

Abbreviations: Arg-1, argenase-1; DSS, dextran sulfate sodium; GPx, glutathione peroxidase; IFN-γ, interferon-gamma; IgE, immunoglobulin E; IL, interleukin; iNOS, inducible nitric oxide synthase; LPA, lysophosphatidic acid; MDA, malondialdehyde; MAPKs, mitogen-activated protein kinases; MCP-1, monocyte chemoattractant protein-1; NF-κB, nuclear factor κB; NLRP3, NOD-like receptor pyrin domain-containning protein 3; NO, nitric oxide; PPAR-r, peroxisome proliferator-activated receptor-gamma; SOD, superoxide dismutase; TNF-α, tumor necrosis factor-alpha.

Table 4
Clinical effects of ginseng and its components for mitigating and managing cytokines.

Materials	Inflammatory Modulators	Effects and Signal Pathway	Assay Models	References
KRGE	↓ Plasma creatine kinase, glucose, insulin, and IL-6	Anti-inflammatory	Uphill treadmill running in humans	[96]
	↑ The number of T cells (CD3) and its subtypes (CD4 and CD8), B cells, and the number of WBC	Immuno-enhancement	100 healthy adults	[95]
	↓ Total IgE, IL-4, and the number of eosinophils in the serum or nasal smears	Anti-allergic	Patients with allergic rhinitis	[99]
Polysaccharide	↑ Th1 cytokines (INF-γ and IL-2); ↓ Th2 cytokines (IL-4 and IL-5); ↑ The ratio of Th1/Th2 cytokines (INF-γ/IL-4 and IL-2/IL-5); ↓ FACT-L scores	Balance of Th1/Th2 T cells	Patients with non-small cell lung cancer	[98]
Ginsenoside-Rg1	↑ Cytokines (TNF-α); ↓ Cytokine (IL-10) in quadriceps muscle	Improving inflammatory balance of skeletal muscle	Healthy men with exercise challenge	[97]

Abbreviations: CD3, cluster of differentiation 3; FACT-L, functional assessment of cancer therapy-lung; IgG, immunoglobulin E; IL, interleukin; Th, helper T cells; TNF-α, tumor necrosis factor-alpha; WBC, white blood cell.

materials might be potential medicinal agents to treat cytokine storm in COVID-19.

6. Conclusions

Here, we discussed physiological and pharmacological potential of *Panax* ginseng and its main active ingredients [(saponin (ginsenosides) and non-saponin)] that could be used to control cytokine storm in COVID-19. *Panax ginseng* is a medicinal plant widely used for the prevention and treatment of various conditions such as infectious diseases. Its positive effects such as immune enhancing, antioxidative, and neuroprotective effects have been demonstrated [8,14]. Accumulating evidence has already suggested the efficacy of ginseng harboring anti-viral potential in *in vitro* and *in vivo* assays and in patients [47,48]. Unfortunately, there are no proven therapeutic interventions available against cytokine storms that can be life-threatening in COVID-19 caused by SARS-CoV-2. Recently, the Chinese government has officially recognized several traditional Chinese medicine formulas such as Lianhuaqingwen, Jinhuaqinggan, and Xuebijing as part of its standard therapy for treating COVID-19 [100]. These reports strongly suggest that natural products have potentials to control COVID-19. Lots of studies have demonstrated that ginseng, a representative herbal medicine, its ingredients, and ginseng-containing prescriptions can beneficially abrogate proinflammatory cytokines (such as IL-1β, IL-6, and TNF-α) and anti-inflammatory cytokines (such as IL-10 and TGF-β) through positive modulation of signaling pathways such as MAPKs, NF-κB, and JAK/STAT [8,14,44–46]. However, further scientific evidences through more preclinical studies and clinical trials are needed to careful use *Panax ginseng* for calming the cytokine storm in COVID-19.

Author contributions

JHC searched and collected literature, summarized contents, and described articles. YHL and TWK organized tables and drew pictures. SKG and SYN provided valuable suggestions during manuscript preparation and critically revised the manuscript. IHC conceptualized and wrote the manuscript. All authors have read and approved the final manuscript.

Declaration of competing interest

The authors have no conflicts of interest associated with this publication. There has been no significant financial support for this work that could have influenced its outcome.

Acknowledgments

This research was supported by the National Research Foundation of Korea (NRF) grant funded by the Ministry of Science and ICT (NRF-2021R1H1A2010055 and NRF-2020R1A5A2019413).

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