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Review

Exploring ginseng's potential role as an adjuvant therapy in COVID-19

Lisa Aielli[1,*], Chman Shahzadi[2,3] and Erica Costantini[4]

[1] Department of Innovative Technologies in Medicine and Dentistry, University "G. d'Annunzio" of Chieti-Pescara, Italy
[2] Center of Advanced Studies and Technology (CAST), University "G. d'Annunzio" of Chieti-Pescara, Italy
[3] University School for Advanced Studies IUSS Pavia, Italy
[4] Department of Medicine and Science of Aging, University "G. d'Annunzio" of Chieti-Pescara, Italy

* **Correspondence:** Email: lisa.aielli@unich.it; Tel: +3908713554026.

Abstract: Ginseng is a plant from the Panax genus used since ancient times as a prominent component of traditional Chinese medicine, and is prized for its energizing, antiaging and antioxidant properties. Over time, the scientific community has taken a keen interest in ginseng's potential as a supplement in various health sectors. While there is a substantial body of data demonstrating the effectiveness of ginseng and other natural products as adjuncts in the treatment of respiratory diseases, the emergence of the COVID-19 pandemic has amplified the attention on ginseng and its extracts as potential antiviral and antibacterial agents. This review aims to summarize the potential benefits of ginseng in the prevention of COVID-19, the alleviation of symptoms and the enhancement of clinical outcomes for patients. It suggests incorporating ginseng and other natural compounds into complementary therapeutic regimens to augment the effectiveness of vaccines and pharmacological treatments. However, it's important to note that further experiments and clinical studies are necessary to solidify the efficacy of ginseng against COVID-19 and to establish its use as a viable option.

Keywords: ginseng; COVID-19; SARS-CoV-2; ginsenosides; immunity modulation; inflammation

1. Introduction

Coronavirus disease 2019 (COVID-19) was first reported in December 2019, as consequence of the pandemic spread of the new coronavirus SARS-CoV-2, which is the causative agent of the acute respiratory disease. Since the first case, the society's health has been severely compromised by COVID-19, thus representing one of the main health issues [1]. In conjunction with the need of specific drugs for the disease, the World Health Organization (WHO) has approved supportive care and complementary and alternative therapies [2,3].

Ginseng, which is a traditional medicine with a history spanning over 2000 years, distinguishes itself as one of the extensively researched herbal supplements. Ginseng contains numerous pharmacologically active ingredients and has been utilized for various conditions. It is frequently employed in treating cardiovascular issues, gastrointestinal disorders, diabetes, as well as autoimmune and allergic respiratory diseases, thereby owing to its modulatory effects on the immune system [4]. Recent studies indicate that ginseng stimulates a robust immune response that offers protection against microbial infections [5]. Moreover, numerous specific clinical studies highlight its positive effects coupled with a low risk of a potential toxicity, thus showing minimal adverse effects under controlled consumption [6,7]. Nevertheless, particular attention is warranted for individuals undergoing treatments with cardiac, antidepressant and antihemorrhagic medications, in which the use of ginseng products may trigger potential side effects [8].

The widely documented use of ginseng in the aforementioned diseases has driven the development of alternative treatments containing ginseng to address COVID-19. This review aims to highlight the potential benefits of ginseng in mitigating the pathogenesis of COVID-19 by summarizing the chemical-physical properties of ginseng and the evidence of its modulatory activities on the immune system, which is highly compromised by SARS-CoV-2. Ginseng could serve as a promising natural compound to complement vaccination and drug treatments against COVID-19.

1.1. Method

To compose this narrative review, research was conducted on PubMed and Google to gather scientific publications concerning the use of ginseng in COVID-19 treatments. The search utilized keywords such as "ginseng", "COVID-19", "SARS-CoV-2", "ginsenosides" and "ginseng and COVID-19". Special attention was directed towards scientific evidence elucidating the modulation of the immune system by both ginseng and SARS-CoV-2, as this constitutes the frontline where the effects of ginseng on COVID-19 manifest.

The authors thoroughly examined, classified and discussed the associated scientific evidence, thus summarizing the corresponding findings.

2. Structural characteristics of ginseng

Ginseng is a perennial plant belonging to the family Araliaceae and genus Panax, and is used worldwide as medicinal and functional herb, with an ancient tradition particularly in China and other Asian cultures [9]. The genus name Panax means "treats all diseases", which was derived from the

Greek words pan (“all”) and axos (“treat”) [10]. In fact, people believed that ginseng could prolong the lifespan [11].

Current studies have reported that ginseng exhibits the following multiple pharmacological activities and therapeutic properties: stress reduction, immunomodulation, antifatigue and antiaging capability have been shown, with positive effects against various diseases, such as diabetes, infections and diverse cancers [12,13].

The word “ginseng” refers to the roots of distinct plant species, of which the most commonly used for their medical and pharmacological characteristics are the Panax ginseng (or Korean ginseng), grown in China and Korea, Panax quinquefolius (or American ginseng), grown in the United States and Canada, and Panax notoginseng (or Chinese ginseng), grown in Southwest China [14–16] (Figure 1).

Figure 1. The origin of pioneering ginseng species in natural medicine.

The bioactivity of ginseng derives from two classes of components: saponins, better known as ginsenosides, and non-saponins [17].

Ginsenosides are a group of triterpenoid saponins that have demonstrated antitumor, anti-inflammatory, antioxidant and antiapoptotic activities, thereby classifying itself as predominant bioactive ingredients of ginseng with medicinal value [18–20]. Ginsenosides consist of a steroidal backbone (17 carbons) with some sugar component generally comprised of hexoses, 6-deoxyhexoses, pentoses or uronic acids. Based on the structure differentiation in carbon skeletons, ginsenosides can be classified into four subtypes: more than 90% of ginsenosides derive from the protopanaxadiol (PPD) class (including *Rb1*, *Rb2*, *Rb3*, *Rc*, *Rd*, *Rg3* and *Rh2* components) and the protopanaxatriol (PPT) class (including *Re*, *Rf*, *Rg1*, *Rg2*, and *Rh1* components); the other two subtypes are oleanolic acid (OA) and ocotillol (OT). This structural variety of ginsenosides contributes to the multiple pharmacological activities of ginseng [21,22] (Figure 2).

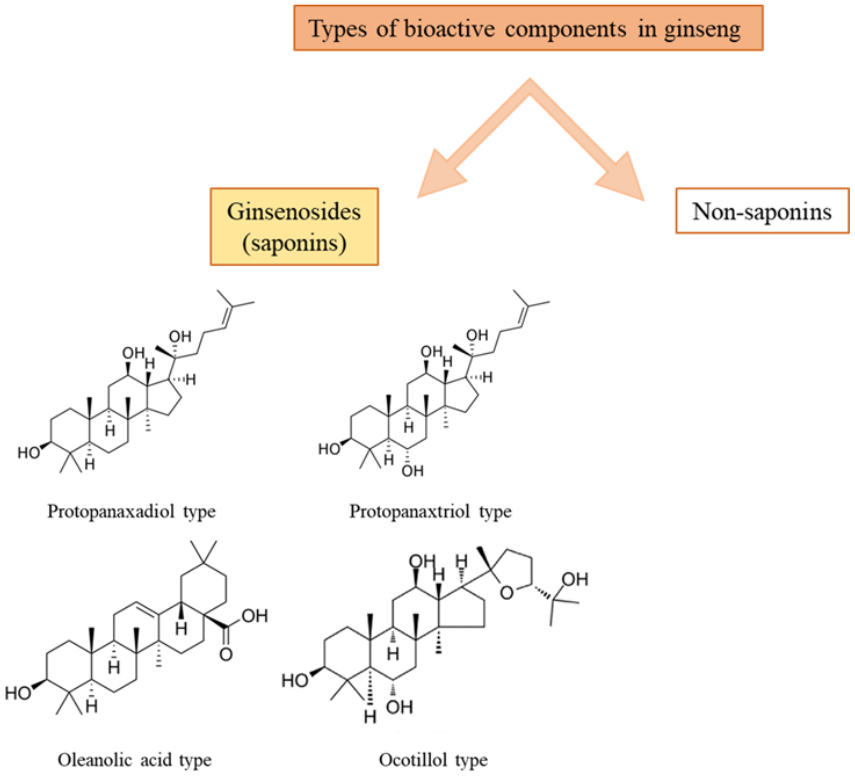

Figure 2. Structure of ginsenosides subtypes.

Ginseng species differentiate in the type and quantity of ginsenosides; moreover, extraction processes and procedures to which ginseng is subjected, such as heating, greatly affect the final quantity of saponins in the specific biotransformed ginseng-based product [9]. The oral administration is not optimal for absorbing ginseng saponins, due to a low membrane permeability and an extensive metabolism in the gastrointestinal tract [18,23]. To maximize the bioavailability of ginsenosides and their therapeutic potential, the stability, permeability and solubility have been enhanced exploring several micro-/nano-sized delivery systems, such as emulsions and vesicular systems [23].

The therapeutic effects of ginseng are not solely mediated by ginsenosides, even though they are major components [18]. Indeed, the non-saponin fraction has been demonstrated to enhance the immune system, delay aging, and inhibit oxidation and inflammation [24]. Non-saponin components of ginseng are classified into saccharide (monosaccharides, disaccharides, trisaccharides, polysaccharides, crude fiber) nitrogen (protein, peptide, amino acid, nucleic acid, and alkaloid) and fat-soluble components (polyacetylene, phenols, essential oils, and phytosterols), as well as water-soluble vitamins and minerals [17] (Figure 3).

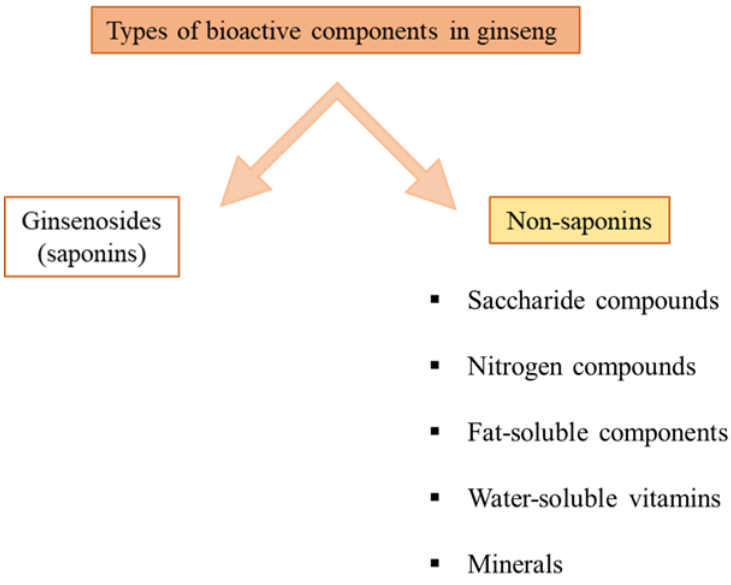

Figure 3. Non-saponin constituents of ginseng.

The numerous pharmacological activities shown from both saponin and non-saponin components of ginseng suggest that both fractions should be studied collectively [17].

3. Ginseng's effects on immune system

Numerous studies report the ability of ginseng to prevent various diseases by regulating the immune system [25]; therefore ginseng is the most frequently used herbal medicine for immune response modulation [26], with either a possible control or stimulating action on each type of immune cell [25].

Ginseng extracts showed the capability to improve innate immunity [27], which is the first line of defense against pathogens and antigens [28] by acting on macrophages, natural killer (NK) cells and dendritic cells (DC) [27]. Moreover, some ginseng components have demonstrated an effectiveness in reviving immune functions weakened by chemotherapy treatment with mitomycin C [10].

Several *in vivo* and *in vitro* studies showed that ginsenosides and other ginseng fractions like polysaccharides exhibit eliciting effects on macrophages' phagocytosis rate, thereby improving the defense from external pathogens [25,29]. In the peritoneal cavity of BALB/c mice treated with different concentrations of a ginseng oligopeptide, an increase of approximately 20% in the rate of macrophage phagocytosis was observed [30]. Additionally, a polysaccharide fraction (ginsan) isolated by Panax ginseng significantly induced cytotoxic activity of murine peritoneal macrophages against B16 melanoma cells in a concentration-dependent manner (macrophages treated with 1-10-100 μg/ml of ginsan for 24h), thus enhancing both the phagocytic action and the secretion of pro-inflammatory mediators by macrophages. As compared to the control, in ginseng-treated macrophages, levels of cytokines involved in the regulation of major histocompatibility complex (MHC), the expression of adhesion molecules and the improvement of immune functions, such as tumor necrosis factor-alpha (TNF-α), interleukin-1beta (IL-1β), IL-6 and interferon-gamma (IFN-γ), were increased, as well as the production of reactive oxygen species (ROS) such as nitric oxide (NO)

and hydrogen peroxide (H_2O_2), probably in correlation with the overexpression of cell surface antigens CD14 (ligand of LPS-binding protein) and I-Ab (MHC class II molecule) [31]. Polysaccharide extracts isolated and purified from Panax ginseng berry and from its dried and steamed roots (called Radix Ginseng Rubra or red ginseng) [32,33] showed the enhancement of pro-inflammatory cytokines IL-6, IL-12 and TNF-α production after stimulation of murine peritoneal macrophages [34] and RAW264.7 cells, respectively [35]. The polysaccharide purified from Panax ginseng by Lim et al., characterized as α(1→6) glucopyranoside and β(2→6) fructofuranoside at 5:2 molar ratio, exhibited potent anti-septicemic activity in C57BL/6J mice infected with *Staphylococcus aureus*, which is attributable to four times an increased production of NO by ginseng extract-stimulated macrophages (0.025 mg/kg body weight of polysaccharide). Treatment of the infection with a combination of ginseng polysaccharide (the same concentration) and antibiotic vancomycin (10 mg/kg body weight) resulted in 100% survival of the animals, thereby suggesting the importance of this natural product as an immunomodulator against sepsis and as a solution to the problem of bacterial antibiotic-resistance [36].

On the other hand, several studies support opposite effects of ginseng on immune response mediators, thus resulting in the inhibition of the inflammatory cascade. One of the best known ginsenosides, *Rb1*, attenuated NO and cyclooxygenase (COX)-2 enzyme levels in THP-1 macrophages and in LPS-treated RAW264.7 cells, thereby reducing the amount of TNF-α and IL-6 protein, as well as their mRNA expression. Likewise, this correlates with the observed *Rb1* ability to interfere with nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) pathways and stop subsequent inflammation [37]. Additionally, the reduction of IL-1, IL-6, TNF-α, NO and free radicals' production mediated by *Rb1* inhibition of the p38/NF-κB-signaling was observed on TNF-α-stressed endothelial cells [38]. *Rb1* also appears to be involved in the regulation of the phosphatidylinositol-3-kinase/protein kinase B/nuclear factor erythroid 2-related factor (PI3K/Akt/Nrf2) signaling pathway, as described by Chen et al. in an *in vivo* intestinal ischemia/reperfusion model. After the injury, *Rb1* administration (15 mg/kg) exerted an attenuation of oxidative stress and pro-inflammatory cytokines by inducing the activation of the PI3K/Akt/Nrf2 pathway through the increase of p-p85 and p-Akt expression levels [39].

Similar characteristics are possessed by Korean ginseng berry extract and several flavonoids derived from ginseng shoots also tested on RAW264.7 macrophages stimulated by LPS: the reduction of NO, inducible NO synthase (iNOS), COX-2, IL-1b, TNF-α and IL-6 mRNA and protein levels, the failure of NF-κB translocation in the nucleus and the inhibition of the MAPK pathway have been observed [40,41].

These results highlight how other ginseng chemical constituents can exert anti-inflammatory and antioxidant activity.

An empowering effect of many ginseng components has also been observed on the activity of NK cells [10], which are the main innate mediators of cellular cytotoxicity [42]. The immunomodulatory effects of ginseng oligopeptides (GOP) on BALB/c mice were studied after intragastric administration. The activity of NK cells 30 days after treatment with GOP significantly increased by 37% and 39% compared to the vehicle control group (deionized water) and by 43% and 45% compared to the whey protein control group in mice treated with GOP 0.0375 and 0.075 g per kg body weight, respectively [30]. The ginseng berry polysaccharide portion (GBPP)-I, obtained by Lee and al. using gel filtration chromatography and consisting of mainly galactose and arabinose, was tested on BALB/c mice by oral and intravenous administration. NK cells of treated mice, tested *ex*

vivo in co-culture with YAC-1 cells, showed an increased cytotoxicity and granzyme B production. Furthermore, the prophylactic action of GBPP-I was observed in mice inoculated with B16BL6 melanoma cells: the lung metastatic activity was significantly and dose-dependently inhibited, presumably by NK cell-mediated antitumor action, as this effect was partially abolished by NK depletion [34]. In a mouse model of lymphoma, a ginsenoside showed the ability to improve the cytotoxic activity of NK cells, thus representing a possible pharmacological aid in the immunotherapy of this type of cancer [43]. Moreover, the same results have been obtained in a model of immunosuppressed mice, where the higher cytotoxicity of NK was accompanied by an overproduction of perforin and granzimes, thus pointing out that ginseng derives immunomodulatory properties other than ginsenosides also from polysaccharidic fractions [44].

Moreover, ginseng extracts have been shown to enhance bone marrow DC proliferation and differentiation [45] as confirmed by the increase of surface co-stimulatory molecules, including MHC class II, CD40, CD80 and CD86 [46].

The activation of DC mediated by some ginseng saponins can induce specific immune responses promoting T cells generation, especially Th1 polarization [47] through the implementation of IL-2 production [48]. The ginsenoside *Rg1* subtype enhances CD4+ T cell activities and modulates Th1/Th2 differentiation. However, ginsenoside *Rg1* promotes CD4+ T cell proliferation and differentiation into Th2 through their IL-4 secretion, thus resulting in a decrease of IFN-γ production [49], just as *Rc* and *Rd* compounds are also involved in the regulation of Th2 cells differentiation and proliferation [50]. Likewise, ginsenoside *Rg3* inhibits the secretion of IL-12 from DC and the subsequent Th1 cell differentiation, thereby reducing IFN-γ expression in T cells [51]. Thus, *Rg1*, *Rg3*, *Rc* and *Rd* ginsenosides are desirable agents for the correction of Th1-dominant pathological disorders. Instead, the *Rb1* ginseng fraction seems to elicit a balanced Th1 and Th2 immune response [52], thus regulating the proportion of T cell subsets by controlling hematopoietic functions, bone marrow stem cells, white blood cells, and T lymphocyte proliferation and differentiation [53].

Therefore, the ginseng ability to shift the production of Th1 and Th2 cytokines may modulate the Th1/Th2 balance in a dosage-, duration of exposure-, route of administration- and composition of the extract-dependent way.

In addition to cell-mediated immunity, ginseng can also regulate the humoral immune response involving B cells and their secreted antibodies. For example, ginsenosides *Rg1* and *20(S)-Rg3* can promote the differentiation of mouse splenic B cells towards IgA specific production when the cells are stimulated with LPS [54].

Therefore, there are many studies in support of the immunomodulatory activity of ginseng and its derivatives on all types of immune cells, and continuous research is carried out so that it can become a pharmaceutical resource in the treatment of diseases and infections in which the immune system is affected.

4. Interplay between SARS-CoV-2 and immune system

SARS-CoV-2 is a positive-sense, single-stranded, RNA virus belonging to the Betacoronavirus genus, which includes viruses affecting the respiratory tract, such as SARS-CoV and MERS, with whom it shares several similarities, especially at the genome level [55–57].

The SARS-CoV-2 genome consists of 14 open reading frames (ORF) and is represented for 2/3 by the 5'ORF (ORF1a and ORF1b), coding for non-structural proteins; instead, the 3'ORF encodes for four structural proteins (membrane (M), spike (S), envelope (E) and nucleocapside (N)) and eight accessory proteins (3a, 3b, p6, 7a, 7b, 8b, 9b, and ORF14) [58]. The S protein, consisting of two domains (S1 and S2), has the functional role of either binding human angiotensin-converting enzyme 2 (hACE2) or transmembrane serine protease 2 (TMPRSS2) on cells' membrane, thereby allowing the virus' entry [56] by receptor-mediated endocytosis. All variants of SARS-CoV-2 present S protein mutations, which confer the property to bypass recognition from antibodies, thereby resulting in an increase of the virus' transmission [59]. From its first decoding, five variants of SARS-CoV-2 have been identified: Alpha (B.1.1.7) in the UK, Beta (B.1.351) in South Africa, Gamma (P.1) in Brasil, Delta (B.1.617.2) in India and Omicron (B.1.1.529), which was first reported in South Africa and then spread to multiple countries. The Omicron variant, which exhibits more than 30 changes in the S proteins, is actually recognized as the most infectious and generates problems for its resistance to vaccines [60].

The mechanism by which the organism reacts to SARS-CoV-2 entry in cells is not completely understood; however, based on the knowledge of other coronaviruses, it has been reported that both innate and adaptive immunity play key roles in the defense of humans. Thus, once inside the cell, SARS-CoV-2 is probably recognized by several pattern recognition receptors (PRR), such as extracellular and endosomal TLR3 and TLR7, or the cytosolic sensors retinoic acid-inducible gene 1 (RIG-I) and melanoma differentiation-associated gene 5 (MDA5) [61], leading to the activation of an inflammatory cascade characterized by the release of type I/II IFN and cytokines such as TNF-α, IL-1β, IL-6 [62]. Through type I IFN receptor (IFNAR) signaling, interferons can activate several molecular pathways, including the signal transducer and activator of transcription (STAT) 1 and 2, thereby achieving a heterogeneous antiviral response [61]. Regarding the adaptive immune response, CD8+ T cells are crucial for avoiding virus' dissemination and CD4+ T cells are responsible for their activation. CD4+ T cells are one of the main type of cells involved both in the early phases of the infection, where they can recognize the S protein (principal target of available vaccines), and in the period following the acute phase [63]. Furthermore, the adaptive immune response is also characterized by the release of antibodies by B cells. In the early phases of infection, IgM and IgA are released and IgG are detectable after 7–10 days. No definitive data are reported about the duration of the IgG response or if the produced antibodies can be considered as neutralizing the infectious agent or protective against infection [64,65].

In severe cases of COVID-19, the innate immune system presents a reduction in the number of NK cells and DC, which are crucial components in the body's response to viral infections. Although the molecular mechanisms are still unclear, it has been observed that, in case of infection, NK cells preferentially move to the lungs and those that remain in the periphery, because of their changed phenotype, promote the virus' spread in the organism. Moreover, a study conducted on 65 hospitalized COVID-19 patients showed not only a long-term loss of DC, but also of their functionality, especially the ability to stimulate T cells [66]; this is consistent with a loss of efficacy of the adaptive immunity. Carsetti et al. identified a reduction of CD8+ naïve T cells and an increased amount of CD8+ terminally differentiated T cells in the serum of patients with a severe diagnosis of COVID-19 [67]. Instead, patients with a moderate clinical outcome present a higher amount of CD8+ T cells but with a less proliferating rate [68]. Thus, in mild and severe cases of COVID-19, it is possible to witness a decrease of CD4+ and CD8+ T cells alongside a decrease of

IL-2 and IFN-γ production [69]: the continuous stimulation of CD4+ and CD8+ T cells is thought to lead to these cells' exhaustion, in accordance with the observed expression of proteins such as the programmed cell death marker 1 (PD-1), the receptor mucin domain-containing protein-3 (TIM-3) and the NK group 2 member A (NKG2A) [70].

Antiviral and immunomodulatory drugs are the two current treatment strategies for COVID-19, and several vaccine platforms (DNA, viral vector, mRNA, protein, inactivated virus) have been developed for its prevention and protection against infection [71]. Given the high mutation rate of the virus' receptor-binding domain (RBD), there is a great interest in the search for alternatives that can potentiate the immune system and work as its adjuvant in addition to vaccines that are specifically directed to the S protein of SARS-CoV-2, including cocktails of many neutralizing antibodies [72] or safer natural substances.

5. Impact of ginseng on SARS-CoV-2 infection

Numerous studies in the literature have demonstrated that ginseng extracts can counteract microbial infections, especially one's caused by viruses, due to their immunomodulatory effects. Ginseng prevents the viral entry into the cells by binding to specific receptors on the cell surface and induces apoptosis within the infected cells by stimulating antibody production and promoting activation of CD4+ and CD8+ T cells [73]. In several *in vitro* and *in vivo* studies, ginseng's properties have been highlighted in the decreasing of pro-inflammatory cytokines, such as IL-1β, IL-6, IL-8, TNF-α, and ROS levels inducted by the virus' spread; moreover, its protective and adjuvant activity of the immune system is explicit with the stimulation of IFN-γ production, thus leading to an effective antiviral mechanism [74]. These multiple ginseng's abilities have been tested on various virus' types, including respiratory ones, such as influenza, respiratory syncytial virus (RSV) and rhinovirus.

For example, ginsenosides can inhibit infection of the influenza virus interacting with the viral hemagglutinin protein, thus minimizing the attachment of the virus with α 2-3' sialic acid receptors on the host cells [75]. In an *in vitro* experiment on DC and macrophages infected by RSV, Korean red ginseng significantly prevented the production of pro-inflammatory TNF-α, IL-6 and IL-8 cytokines; moreover, in a murine model subjected to RSV infection, pre-treatment with Korean red ginseng at a dosage of 4 mg per mouse resulted in an improved clearance of the virus in the lungs. This improvement was associated with a heightened production of IFN-γ in bronchoalveolar lavage cells, along with an increased abundance of CD8+ T cells and DC [76]. Furthermore, in the context of RSV immunization, oral administration of ginseng led to an increase in antibody responses to the vaccine associated with a decrease in IL-4 and an increase in IFN-γ levels, thereby effectively improving the protection against RSV infection [77]. Yoo et al. showed that Korean red ginseng extract significantly increased the survival of mice infected with H1N1 and H3N2 influenza viruses, thereby lowering levels of viral titers and IL-6 [78].

Therefore, taken together, these studies highlight the potential abilities of ginseng to interfere with the success of viral infections. Indeed, ginseng has a remarkable action in blocking the virus' entry into cells, thus preventing the virus' replication and modulating inflammation, which is the main event responsible for severe clinical manifestations.

Considering this evidence, it is plausible to think that supplementation with ginseng can be useful for the prevention or mitigation of serious secondary consequences deriving from virus

infection; indeed, in animal experiments, ginseng has increased the defense against secondary pneumococcal pneumonia, which is one of the complications of SARS-CoV-2 infection [79].

These ginseng properties could prove advantageous in the context of SARS-CoV-2, which shares a good similarity in pathogenicity with other viruses, thus preventing infection, strengthening the antiviral response and reducing complications due to persistent inflammation.

The oral uptake of ginseng could protect the body from the entry and proliferation of SARS-CoV-2 by binding to the ACE2 receptor, which is one of the entry receptors of the coronavirus, as suggested by an *in silico* approach [80]. In a mouse model, when ginseng was administered to mice susceptible to COVID-19, a 30% chance of survival was observed in the ginseng-administered mice, whereas all the mice of non-ginseng group died. Thus, the administration of ginseng significantly increased the survival rate and decreased the viral concentration in the lungs by inducing antiviral IFN-γ compared to the non-ginseng administered controls [81].

Several *in vitro* and *in vivo* studies showed that ginseng extract inhibits the production of various pro-inflammatory cytokines and elevates the production of anti-inflammatory cytokines [82–84]. Ginseng may regulate the production of pro-inflammatory mediators, including IL-8, which, in turn, stimulates the hyper-activation of neutrophils [85], IL-6, which is linked with severity and disease course of severe COVID-19 [86], and ROS, whose excessive production can also be associated with neutrophil function deregulation, and therefore can be the cause of progression towards a more aggravated clinical picture [87]. In murine model of sepsis [88], asthmatic mice and lung epithelial cells [89], the ginsenoside *Rg3* subtype showed the anti-inflammatory ability [88,89] mediated by the inhibition of NF-κB and MAPK pathways [88]. In a rat model of myocardial infarction, *Rg3* can reduce the serum concentration of TNF-α, IL-1β and IL-6 acting on sirtuin protein SIRT1, which is a cell stress sensor responsible for the repression of NF-κB and its downstream cascade [90]. Underlining the possible use of ginseng's compounds to control and reduce human disorders like pulmonary disease and myocardial infarction by alleviating inflammation and improving tissue recovery and regeneration, these results suggest that ginseng would potentially be able to restore the efficiency of many molecular pathways that are up-regulated by SARS-CoV-2, including that of NF-κB and MAPK involved in promoting a constant inflammatory status [91].

Ginseng and its major active constituents, ginsenosides, show potential preventive and therapeutic roles in COVID-19 by targeting inflammasome stimulation and inflammasome-mediated inflammatory signaling pathways activated by SARS-CoV-2, thereby improving the immune system and exerting anti-inflammatory effects [92]. Korean red ginseng can inhibit the NLR family pyrin domain containing 3 (NLRP3) inflammasome sensor, either directly or indirectly affected by SARS-CoV-2, which drives NLRP3 inflammasome assembly and inflammatory caspase activation, thus culminating in the disruptive inflammation of severe COVID-19 [93,94]. Hence, ginseng may represent a potential therapeutic agent to alleviate and manage persistent hyperinflammation resulting from COVID-19-mediated cytokine storms and inflammasome activation, thereby reducing clinical manifestations and avoiding multiple organ failure and death. The study of Feng et al. [95] observed that, in a cohort of 118 COVID-19 patients, the administration of a therapy composed of a herb mix, with ginseng as the main component, gave a reduction in virus-induced production of pro-inflammatory cytokines and in the mortality rate, thus improving the outcomes of serious and critical patients.

Lastly, ginsenosides have been shown to facilitate the development of higher levels of specific antibodies, thus becoming possible candidates as adjuvants in vaccines against several invading

microorganisms, such as Salmonella, *Toxoplasma gondii* and influenza virus [96–98]. Korean red ginseng displayed a clinical effect on COVID-19 specific antibodies after COVID-19 vaccination, thereby maintaining higher anti-S and anti-N antibody titers compared to the untreated group [99] (Figure 4). Table 1 summarize the effects of ginseng on viral and respiratory diseases previously discussed.

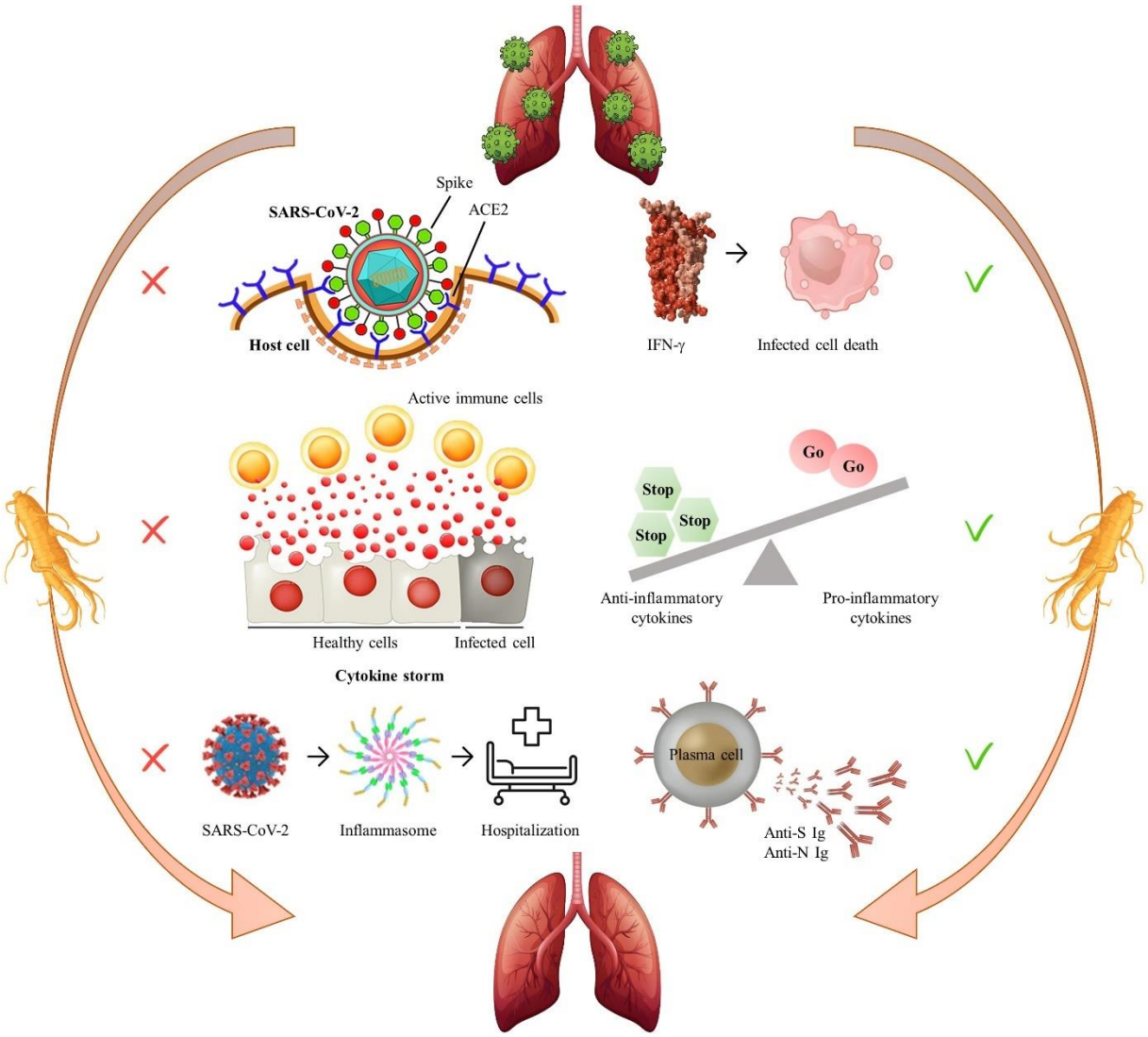

Figure 4. Summary of ginseng's impact on SARS-CoV-2. Ginseng exhibits a range of actions in combating SARS-CoV-2 infection and the development of COVID-19. It employs various mechanisms to hinder viral processes, such as binding to the ACE2 receptor to prevent viral entry into cells and dampening the virus-triggered cytokine storm and inflammasome activation (on the left). On the other hand, ginseng actively encourages antiviral mechanisms, including the stimulation of IFN-γ production, boosting the generation of anti-inflammatory cytokines, and enhancing the antibody response directed at viral components S and N (on the right).

Table 1. Ginseng's effects on viral and respiratory diseases.

Reference	Type of ginseng	Health issue	Biological effects
Dong W et al. (2017) [75]	Rb1 ginsenoside	Influenza A (H1N1) virus	Prevention of virus attachment with α 2-3' sialic acid receptors on host cell surfaces
Lee JS et al. (2015) [76]	Korean red ginseng extract	Respiratory syncytial virus (RSV)	-Reduction of TNF-α, IL-6 and IL-8 from RSV-infected DC and macrophages -Increase of IFN-γ, CD8+ T cells and DC from infected murine model
Lee JS et al. (2014) [77]	Korean red ginseng extract	Respiratory syncytial virus (RSV)	Increase of antibodies production and IFN-γ levels, decrease of IL-4, in immunized mice
Yoo DG et al. (2012) [78]	Korean red ginseng extract	H1N1 and H3N2 influenza viruses	Reduction of lung viral titers and IL-6, increment of IFN-γ levels, in infected mice
Boopathi V et al. (2023) [80]	K ginsenoside	SARS-CoV-2	Inhibition of viral entry into host cells, binding to the ACE2 receptor (*in silico*)
Seo SH (2022) [81]	Korean ginseng extract	SARS-CoV-2	Decrease of lung viral concentration and induction of IFN-γ, increasing the survival rate of mice with COVID-19
Huang WC et al. (2021) [89]	Rg3 ginsenoside	Asthma	Reduction of anti-oxidative stress and inflammation in asthmatic mice and tracheal epithelial cells
Feng J et al. (2021) [95]	Shenhuang Granule with Panax ginseng fraction	SARS-CoV-2	Reduction of organ dysfunction, mechanical ventilation, hospitalization and mortality in severe patients with COVID-19
Xu ML et al. (2012) [98]	red ginseng (RG) extract and RG saponin	Influenza A (H1N1) virus	Increment of serum anti-influenza A virus IgG titers and improvement of survival rate in immunized mice
Rhee DK (2022) [99]	Korean red ginseng	SARS-CoV-2	Anti-S and anti-N antibody titers maintenance in COVID-19-vaccinated subjects

ACE2: angiotensin-converting enzyme 2; COVID-19: coronavirus disease 2019; DC: dendritic cells; H1N1: influenza A virus subtype H1N1; H3N2: influenza A virus subtype H3N2; IFN: interferon; Ig: immunoglobulin; IL: interleukin; N: nucleocapside; RG: red ginseng; RSV: respiratory syncytial virus; S: spike; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; TNF: tumor necrosis factor.

6. Ginseng's mitigating effect on COVID-19 complications

Evidence is available for the effectiveness of ginseng in either counteracting or alleviating the wide spectrum of clinical complications related to COVID-19.

It has been proposed that ginsenosides could prevent the heart diseases of COVID-19, characterized by myocarditis, acute myocardial infarction and arrhythmias, by interacting with the binding of SARS-CoV-2 S protein to the myocardium and regulating the membrane potential of cells, thus protecting the heart from the intracellular invasion of the virus and maintaining the correct rhythm of muscle contraction [100,101].

Ginseng administration could regulate the thrombosis and platelet aggregation cascade during the pathogenesis of COVID-19, thereby playing an important role in the prevention of vascular damage and its consequences [102,103]. Abnormal blood coagulation due to SARS-CoV-2 infection is contrasted by antiplatelet activities of the subtypes *Rp1*, *Rp3*, *Rp4* ginsenosides, which are effective in preventing the activation of integrin αIIbβ3, the binding of fibrinogen to integrin αIIbβ3, and formation of aggregates [104]. An *in vivo* study showed that ginsenoside *Rg3* reduces thrombus formation [105]. Yi et al. [106] reported that an extract of total ginsenosides elevated coronary perfusion flow by the activation of PI3K/Akt-eNOS signaling and NO production, with possible applications in preventing or treating ischemic events. Increased thromboxane (TX) A2 levels, which were quickly converted into TXB2, were reported in patients with COVID-19, alongside hypoalbuminemia, the increased risk of venous thromboembolism and the hypercoagulability, which were inhibited by red ginseng [107]. Ginseng extract was found to significantly improve NO synthesis in animal experiments. Kim et al. reported that ginsenoside inhibited free radical damage in blood vessels in the lung tissue by increasing NO secretion that could protect vascular function [108].

There is some evidence that SARS-CoV-2 infection may determine acute kidney injury. Although there is not much evidence, it is plausible to think that the administration of ginseng may also be useful in preventing and restoring normal kidney functions [109,110].

Taken together, these findings suggest the potential beneficial effects of ginseng against cardiac, vascular and renal complications of COVID-19.

Lastly, another aspect that can be taken into consideration, in the relation between ginseng and COVID-19, is the energy support given by orally consuming ginseng, especially thanks to ginsenosides. Indeed, the administration of HRG80, which is a unique red ginseng with highly concentrated rare and noble ginsenosides [111], leads to a 67% energy recovery, an improvement in sleep quality and a decrease in the amount of pain feeling [112], thereby resolving the common syndromes of fatigue and fibromyalgia exhibited by COVID-19 patients.

7. Conclusions

Ginseng is one of the most investigated medicinal plants for its historically known healing properties. Its ever-increasing consumption as a food supplement has increased the interest in ginseng's putative functions in the treatment of complex diseases, such as diabetes mellitus and gastrointestinal disorders [113,114], as well as in its ability to interact with the immune system [25]. The capacity to act as a regulator of the immune system has led to considering ginseng as a therapeutic agent in autoimmune diseases [115], such as rheumatoid arthritis [116], allergic

respiratory disease and asthma [32]. Recently, several studies have shown that ginseng promotes a vigorous immune response that protects against bacterial, fungi and viral infections [74,117,118].

The WHO officially declared the COVID-19 pandemic on March 11, 2020 [119]. Although the state of emergency has since concluded, COVID-19 remains a global challenge, thereby placing a significant strain on healthcare systems and national economies.

As of September 24, 2023, there have been over 770 million confirmed COVID-19 cases and more than 6 million reported deaths worldwide [120]. Additionally, the circulation of several variants has been documented. Since 2020, impressive research efforts in developing COVID-19 vaccines have yielded several effective options. These vaccines have significantly alleviated the growing pressure on healthcare systems by reducing viral transmission and infection rates, as well as the incidence of hospitalizations due to severe COVID-19 complications [121].

However, there is still a need to focus on the development of potential drugs for the treatment of patients with severe clinical symptoms. Recent knowledge on the pathogenesis of SARS-CoV-2 has largely improved the planning of therapeutic strategies for the management of COVID-19, with different antiviral and immunomodulatory drugs under investigation, although specific therapies are not yet available.

Given the growing use of plant ingredients, which are considered safer and less expensive than synthetic products [122], and several studies demonstrating the consolidated activity of a large list of natural extracts against viral pathogens (like hepatitis, influenza, herpes simplex, entero- and corona-viruses) [123], several compounds of a natural origin have been proposed that can help to control the infection and the most serious clinical complications from SARS-CoV-2. Among these, the study of ginseng as a beneficial supplement in the management of COVID-19 is of a wide interest. To date, this plant seems to be the most accredited for its antiviral properties as a possible adjuvant agent, not only for vaccination, but also for therapy, thanks to its ability to act in restoring the functions of the immune system compromised due to SARS-CoV-2 infection, despite the need for further clinical trials to demonstrate its efficiency and safety. To use ginseng extracts more effectively, a greater understanding of the interaction between its main pharmacologically active components and SARS-CoV-2 would be necessary, thereby bringing the pathways involved in its antiviral action to light and a greater amount of clinical data will support its real adjuvant and therapeutic efficacy.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Conflict of interest

The authors declare no conflict of interest.

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