

Contents lists available at ScienceDirect

Journal of Ginseng Research

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



Review Article

Ginseng, a promising choice for SARS-COV-2: A mini review



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ARTICLE INFO

Article history:

Received 29 December 2021

Received in revised form

15 January 2022

Accepted 16 January 2022

Available online 22 January 2022

Keywords:

Korean ginseng

SARS-CoV-2

Anti-viral immunity

Anti-viral activity

ABSTRACT

The current Covid-19 pandemic has changed the entire world and brought so many unprecedented challenges to the scientific community. More than 5 million people died due to the SARS-COV-2 outbreak. For many thousands of years, ginseng, the traditional herb has been used for various infectious diseases by traditional healers. Ginseng showed promising antiviral effects by modulating both natural and acquired immunity. Ginseng might be used as a potential therapeutic agent to prevent SARS-CoV-2 infection along with the vaccine. In this current review, we offer an alternative approach for SARS-CoV-2 prevention during this unprecedented pandemic.

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1. Introduction

SARS-CoV-2 caused significant casualties with huge social and economic impacts all over the world, and it imposed unprecedented challenges in the entire health systems of the world [1]. The Covid-19 has affected all the territories of the world, since its first appearance in Wuhan, China [2,3]. SARS-CoV-2 is a single-stranded, positive-sense, RNA-enveloped virus [4]. In the recent past, Ebola, Zika and SARS viruses also brought considerable attention to the scientific community [5]. The “Black death” (plague) from the fourteenth century or the “Spanish Flu of 1918” has had profound effects on society’s human history [6]. Despite many challenges, the discovery and development of the SARS-CoV-2 vaccine are remarkable, however, still, there is lack of standard pharmaceutical cure for this deadly infection [7]. However, with conventional therapies, the use of traditional medicines can play a

pivotal role in Covid treatment. China, Korea, and some of the African countries have had a long standing tradition of using herbal medicine [8,9]. Interestingly, ginseng, “the king of all herbs”, might play a significant role during Covid-19 infection as it can modulate both natural and acquired immunity during viral infection [10].

Traditional use of ginseng could be traced for thousands of years in China and Korea [11]. Ginseng belongs to the Araliaceae family, however, it has more than eight to thirteen species under this genus, and among those the *P. ginseng* is commonly used, widely famous as “Asian or Chinese ginseng”. Interestingly, the word “Panax”, named after the Greek word “panacea,” which means “the cure for all diseases” [12]. Studies suggested active components of ginseng, ginsenosides can act as anti-viral or anti-bacterial agents [10,13]. Different *in vitro* and animal studies revealed the antiviral action of ginseng (Table 1). The influenza A or B viruses are most common cause of seasonal flu [14]. One study revealed that red ginseng could be helpful in preventing this lethal infection of the H5N1 influenza virus [15]. Interestingly another study found that ginsenosides can act as a mucosal adjuvant against the influenza virus [16]. One clinical study suggested that ginseng can induce genetic defects in the nef gene in AIDS (acquired immunodeficiency syndrome) patients [17]. Moreover, the study found that

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Table 1
Antiviral effect of ginseng.

Viral Infection	Study type	Sample	Result	Ref.
Human immunodeficiency virus (HIV)-1	Clinical study	Red ginseng extract	Combination with zidovudine (antiretroviral medication) showed promising antiviral effects by preserving CD4 ⁺ T cell counts	[19–21]
Hepatitis B virus	In vitro study	Ginsenoside Rg3	The secretion of HBsAg, HBeAg in HBV-infected HepG2.2.15 cells was inhibited by ginsenoside Rg3	[18]
Hepatitis A virus	In vitro study	ginsenosides Rb1 and Rg1	ginsenosides Rb1 and Rg1 decreased the HAV titer	[22]
Rotavirus	In vitro study	hot water extract of ginseng	Pectic polysaccharides from <i>Panax ginseng</i> inhibited rotavirus infection	[23]
Influenza virus	In vitro study, in vivo study	Korean Red Ginseng (KRG)	Ginseng treatment can improve the viability of human alveolar epithelial A549 cells	[24]

ginsenoside Rg3 can inhibit the JNK/AP-1 signaling in Hepatitis B virus-infected HepG2.2.15 cells [18].

The SARS-CoV-2 virus is continuously mutating as the countries are racing to vaccinate people as fast as possible. Pneumonia is the common complications of SARS-CoV-2 infection. This infection attenuates body's immune system as a result pneumonia occurs. Previous scientific evidence suggests the antiviral properties of ginseng, which could be effective against Covid 19 as well. Ginseng could act as an adjuvant in SARS-CoV-2 by modulating both natural and acquired immunity.

2. Impact of ginseng on immunity

Ginseng is well-known for its adaptogenic response to immune functions [25,26]. Innate immunity which is regarded as the body's initial line of protection against numerous infections. This immunity refers to nonspecific defensive mechanism mediated by a varied range of receptors from multiple protein families [27]. This immune system involves both physical and chemical barriers. Macrophages act as an effector cell in the innate immune system that are capable of secreting both antimicrobial and pro-inflammatory mediators [28]. Studies found that ginseng showed the immunomodulatory effect on macrophage, the wild ginseng extract can upregulate the Nitric oxide (NO) production, and the cytokines production including IL-1 α , IL-1 β , IL-6, TNF- α , and granulocyte-macrophage colony-stimulating factor [29]. Ginseng can increase the phagocytic activities of the reticuloendothelial system and showed potential antitumor effects against sarcoma in animal model [30]. Ginsan, a fraction of *P. ginseng*, also showed immunopotentiation effect on peritoneal macrophages [31]. Dendritic cells (DCs), play an important role in linking with innate and adaptive immune system, and these cells are responsible for antigen-specific immune responses [32]. Ginseng also showed immunomodulatory effects on DCs, one study found that it can suppress the cytokine production and also the maturation of LPS-treated DCs with downregulating the CD4 (+) T cells [33]. Another study revealed that it can enhance the surface co-stimulatory molecules, including MHC class II, CD40, CD80, and CD86, on bone marrow-derived DCs (BMDC) [34]. Natural killer (NK) cells play a pivotal role in innate immune responses by combating infection [35]. Study found that *P. ginseng* can increase the natural killing activity in animal model [36,37]. Another clinical study revealed that *Panax ginseng* can significantly enhance the NK cells in AIDS patients [38].

Adaptive immunity is a type of defensive mechanism that offers a more specialized store of recollection for both self-antigens and foreign antigens. This response mechanism emerged from immunologic memory and is characterized by tightly controlled communication between antigen-presenting cells and lymphocytes. Lymphocytes' characteristic fighters are B and T cells, which are continually created from progenitor stem cells found in the

bone marrow and thymus [35]. Ginseng also showed immunomodulatory effects on the cell-mediated immunity, study found that the red ginseng extract can immunosuppress the regulation in animal model by promoting IFN- γ + CD4 + T cells, IFN- γ T cell (reg) production [39]. Different studies also revealed that ginseng can significantly increase the antibody-dependent cellular cytotoxicity and NK cell activity in *in vitro* and *in vivo* studies [40]. One *in vivo* study attributed that the Rb1, fraction of ginseng adjuvanted vaccine can stimulate the titers of antigen specific IgG1, IgG2a and IgG2b and helped in balancing Th1 and Th2 immune response [41].

3. Potential of ginseng in treating SARS-CoV-2

Researchers used different computational techniques to investigate a natural chemical ingredient of ginseng as a potential inhibitor of the primary protease of SARS-CoV-2. Fallah et al.(2021) [42] used seven compounds from *Panax ginseng* and performed molecular docking, the glide docking program (Table 2). Flor-alginoside B extracted from *Panax ginseng*, showed promising binding affinity (-8.618 kcal/mol) with the receptor-binding domain of SARS-CoV-2. This could be a potential candidate for combating the SARS-CoV-2 infection. Han et al. [43] investigated Shenmai Injection's (consists of red ginseng + ophiopogon japonicus) molecular interaction network route in the treatment of COVID-19 patients having heart disease and they found that Shenmai Injection can be effective in treating COVID-19 by reducing cytokine storms. Li et al. [44] used Shenfu decoction to treat patients with severe COVID-19 and the study revealed that, it could play an essential role in regulating the anti-viral process, regulating immunity, and reducing inflammation. Moreover, Wang et al. [45] found that the active chemicals in Shengmai injection (consists of red ginseng, ophiopogon japonicus, and schisandra chinensis) can modulate several signaling pathways including CASP3, PTGS2, NOS2, NOS3 which might play a pivotal role in COVID-19 treatment. Furthermore, another study [46] proposed that *Panax ginseng* can reduce chronic fatigue syndrome and Fibromyalgia, the common symptoms of COVID-19. Again, Han et al.(2021) [47] experimented with fermented Ginseng (black) and reported that it not only stops SARS-CoV-2 from replicating in the cell, but it also lowers the quantity of viral RNA (vRNA) copies floating around in the extracellular environment.

4. Ginseng as an adjuvant

Adjuvants are compounds or components that can improve vaccine efficacy [49], ginseng and its ingredients ginsenosides could be potential adjuvants to improve Covid infection. Previously, *P. ginseng* has been used to improve immunity, memory, menopausal symptoms, cardiovascular dysfunction, neurological disorder [12,50–52]. The human immune system is a complex network that defends the body from different infections. Poor nutrition,

Table 2
Antiviral components in ginseng.

Country	Compounds	Study Type	Findings	Ref.
Iran	Seven compounds from <i>Panax ginseng</i>	Molecular docking, Glide docking program.	Floralginsenoside B extracted from <i>P.ginseng</i> , showed promising effect, it had strong binding affinity with the receptor-binding domain of SARS-CoV-2.	[42]
China	Shenmai Injection (Red ginseng + ophiopogon japonicus)	Network pharmacology	Shenmai injection can treat COVID-19 by reducing cytokine storms, demonstrating a network control mechanism of mutual influence and complicated correlation.	[43]
China	Shenfu decoction (water extract of the dried root of <i>Panax ginseng</i>) + root of Aconitum carmichaeli Debx	Network pharmacology	To treat patients with severe COVID-19, shenfu decoction played an essential role in regulating the anti-virus process, regulating immunity, and reducing inflammation.	[44]
China	Shengmai injection (Red ginseng + ophiopogon japonicus + schisandra chinensis)	Network pharmacology and Molecular docking	The active chemicals in Shengmai Injection modulate several signaling pathways for anti-inflammatory, immunological modulation, anti-shock, and boosting blood oxygen saturation, all of which may play a role in COVID-19 treatment.	[45]
United States of America	<i>Panax ginseng</i> root extract (HRG80™ Red Ginseng)	Prospective study	People suffering from chronic fatigue syndrome and Fibromyalgia (symptoms of COVID-19) yield significant improvement	[46]
Korea	Fermented <i>Panax ginseng</i> (Black)	In vitro	Ginseng lower the quantity of viral RNA (vRNA) copies floating around in the extracellular environment.	[48]

certain chronic conditions, burn and drugs can weaken our immune system [53,54]. Natural products are the good source of phytochemicals which are capable of enhancing immune function [10]; interestingly, ginseng has been shown to use as a dietary supplement that can also enhance both types of immunity [55–57].

For example, orally administered ginseng leaf-stem saponins (GSLS) in combination with a live infectious bursal disease vaccination improved both humoral and gut mucosal immune responses in chickens [58]. In other studies, ginsan, a polysaccharide extracted from *Panax ginseng*, showed different immunomodulatory effects

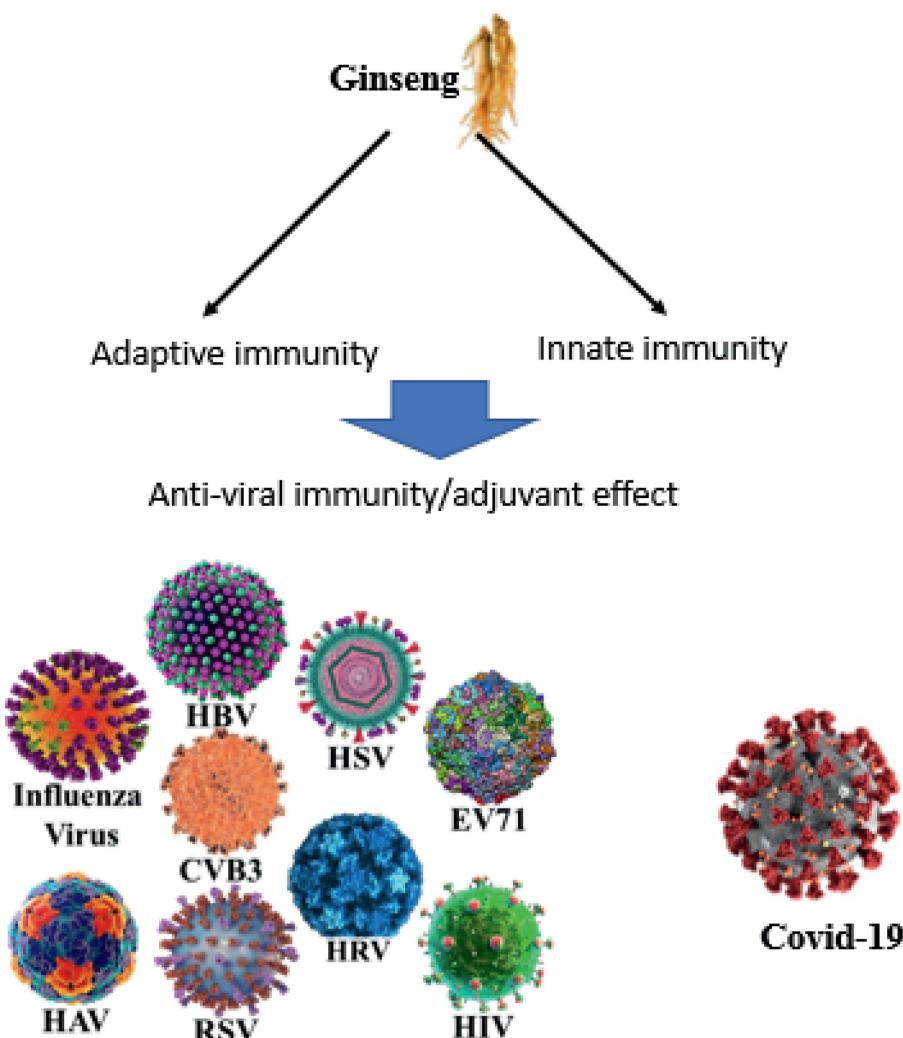


Fig. 1. Schematic diagram of anti-viral activity by Korean ginseng. Ginseng is a potent anti-viral agent by enhancing innate and adaptive immunity and adjuvant action.

by inhibiting the nuclear factor-kappa B (NF- κ B) pathway and p38 MAP kinase [59]. Moreover, studies narrated the anti-inflammatory effect of ginseng [60–63]. Different adjuvants like toll-like receptor (TLR) agonist, aluminum salt, and emulsions have been used for vaccine formulations in animal models [64]. In this current situation, ginseng should be a choice of adjuvant during Covid infection.

5. Conclusions

The Covid-19 pandemic has posed a serious public health threat in the form of a deadly pandemic. To combat this deadly SARS-CoV-2, it is important to identify promising and successful targeted tactics. Apart from chemical and allopathic medications, naturally occurring compounds can play a pivotal role as antiviral agents. The pathogenesis of SARS-CoV-2 is similar to that of other viral infections. Taken together, according to the previous finding, ginseng is a potent anti-viral agent by enhancing innate and adaptive immunity and adjuvant action (Fig. 1), so it could be a game-changer in Covid treatment, however, clinical trials studies are required for further development.

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgements

This research was funded by the Basic Science Research Program through the National Research Foundation of Korea (NRF), the Ministry of Science and ICT, South Korea (2017R1A6A1A03015642) and also supported by the Korean society of ginseng (2020), South Korea.

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