



## Review Article

## Possibility as role of ginseng and ginsenosides on inhibiting the heart disease of COVID-19: A systematic review



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## ABSTRACT

Coronavirus has been spreading rapidly around the world since it broke out in China in 2019. Respiratory diseases caused by coronavirus infection cause various diseases ranging from asymptomatic subclinical infections to severe pneumonia and cardiovascular complications, leading to death. In this regard, natural products are being studied to prevent various diseases caused by COVID-19. In current review, we would like to present mechanisms related to the inhibition of heart disease in ginseng and ginsenoside against SARS-CoV-2. In many previous studies, ginseng and ginsenoside are known to have antioxidant, blood flow improvement, improvement of vascular and heart function, blood pressure control, suppression of myocardial infarction and heart failure, and antiarrhythmia. Therefore, ginseng and ginsenoside have a possibility to suppress cardiovascular complications caused by COVID-19. Many of research provide evidence for ginseng and ginsenoside as treatments for the risk of cardiovascular complications. However, in this review, more specific contents on the proposition of the efficacy of ginseng and ginsenoside for COVID-19 should be presented. Therefore, we hope that researches to reduce cardiovascular complications of ginseng and ginsenoside for COVID-19 should be presented to reduce mortality for COVID-19.

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## 1. Introduction

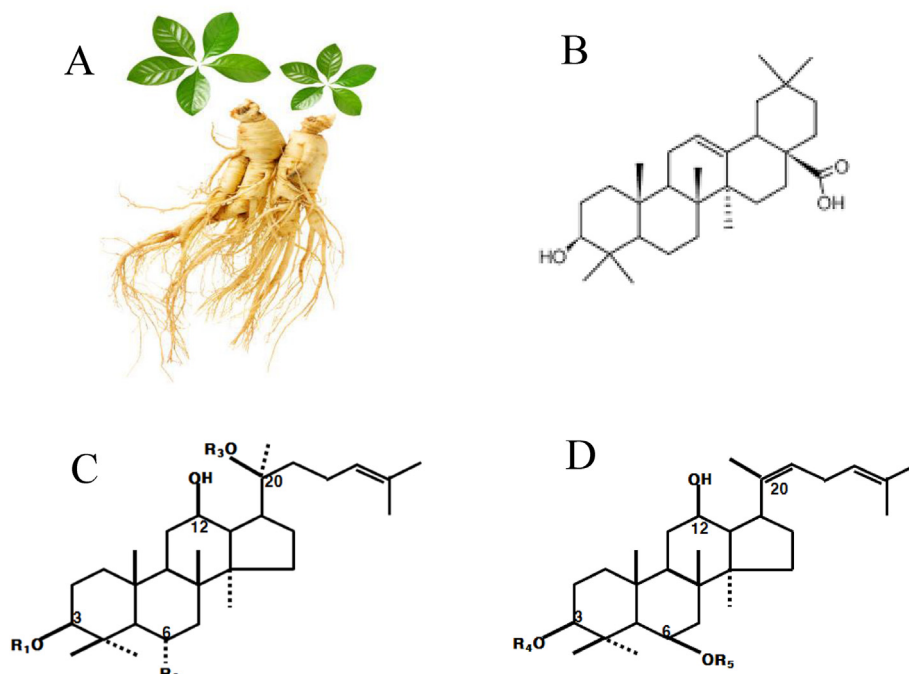
The pandemic of COVID-19, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which recently occurred in China, is highly contagious, threatening human health and causing serious emergencies for public health around the world [1]. SARS-CoV-2 was detected the most in the lungs, but significant amounts were also detected in the heart, kidneys, and liver. COVID-19 viruses were also detected in heart tissue in 16 out of 22 deaths with SARS-CoV-2 [2]. Therefore, SARS-CoV-2 can directly or indirectly cause lesions in the heart, causing abnormal heart function. In addition, the SARS-CoV-2 is known to be infected with heart cells and cause arrhythmia and heart failure, causing very fatal damage to health [3]. Recently, an autopsy of 39 patients who died of COVID-19 revealed a very large amount of virus in the heart in 31% of patients [4]. Moreover, COVID-19 exacerbated cardiovascular disease (CVD) and caused heart complications that could cause serious health damage [5]. When infected with COVID-19 virus,

necrosis of heart cells occurs, leading to a variety of cardiovascular complications, ranging from fatal diseases such as heart failure, in which the heart cannot pump sufficient blood. These heart complications are one of evident in COVID-19 virus infection, and heart dysfunction is caused by COVID-19 complications, such as cardiomyopathy, heart ischemia, and arteriosclerosis associated with thrombosis [3].

Ginseng (or ginsenosides) has been widely used in Oriental traditional medicine and has become increasingly popular in the Western world for its tonic effect and various therapeutic effects on cardiovascular, central nervous system, and endocrine. It was well known that *Panax ginseng* is one of the most commonly greatly used species of ginseng. For thousands of years, Generally, among the diverse ginseng species, *Panax ginseng* (Korean ginseng), *Panax notoginseng* (Chinese ginseng), *Panax quinquefolius* (American ginseng) and *Panax japonicum* (Japan ginseng) are the most common [6]. Most of research on the pharmacological and therapeutic functions of *Panax ginseng* has chiefly focused on ginsenosides [7]. Ginsenosides, an active compounds of ginseng, can be classified into oleanolic acid type, protopanaxadiol type, and protopanaxatriol type based on the chemical structure (Fig. 1 and Table 1).

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**Fig. 1.** Panax ginseng Meyer herb and chemical structures of ginsenoside-subtypes. The picture of *Panax ginseng* Meyer (A). Molecular structures of protopanaxadiol-type (B), protopanaxatriol-type (C), and oleanolic acid-type (D).

**Table 1**  
Classification of ginsenosides.

Subtype	Ginsenoside
Oleanolic acid	Ro
	Ri
	Rh3
Protopanaxadiol (PPD)	Compound K (CK)
	Ra (1,2,3)
	Rb (1,2,3)
	Rc
	Rc
	Rg3
	Rh2
	F2
Protopanaxatriol (PPT)	F1
	Rg (1,2)
	Re
	Rf
	Rh1

In this regard, studies have been reported on the heart protection of ginseng or ginsenosides over the past few years, especially the effect of protecting the heart from the occurrence of myocardial infarction. This has been widely reported in ginseng components such as ginseng extracts [8,9], ginsenoside Re [10], ginsenoside Rb1 [11–14], and ginsenoside Rg1 [15,16]. Studies showing that ginseng and ginsenoside are pharmacologically therapeutic for cardiac dysfunction have been reported using animal models [8–16]. In such studies ginseng or ginsenoside very significantly indicates that it protects the heart by preventing heart failure. Above all, COVID-19 virus enters the heart through ACE2 receptors, causing acute cardiac injury and provides many evidences of cardiovascular complications, such as systemic inflammation, coronary artery disease, heart failure, heart arrhythmia, myocardial ischemia, and intravascular thrombosis. Therefore, the present review aims to scientifically provide the possibility for prevention of cardiac

complications with ginseng and ginsenosides in COVID-19 infection, to help find ways to lower the mortality from COVID-19 [1].

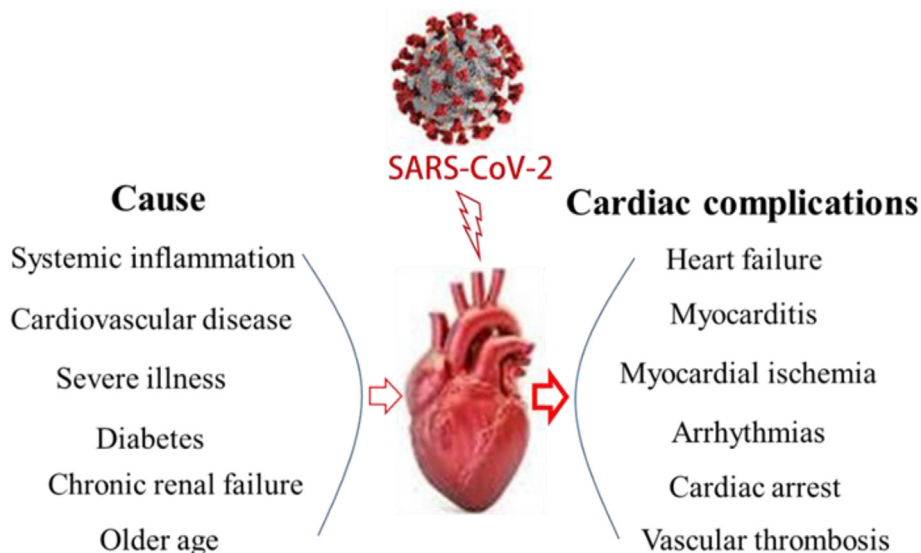
## 2. Panax ginseng and ginsenosides against cardiac pathogenesis of COVID-19

SARS-CoV-2, which was first reported in China in 2019, mostly shows mild to moderate symptoms. However, sometimes SARS-CoV-2 infections progress to severe organ damage and severe pneumonia in about 15% of SARS-CoV-2 infections, and about 5% eventually develop septic shock and multiple organ dysfunction, such as heart and lungs, which has a fatal on life [4]. Respiratory diseases usually occur during SARS-CoV-2 infection, but cardiovascular complications are caused by various mechanisms. The mechanism of cardiovascular complications caused by COVID-19 infection is as follows [17] (Fig. 2).

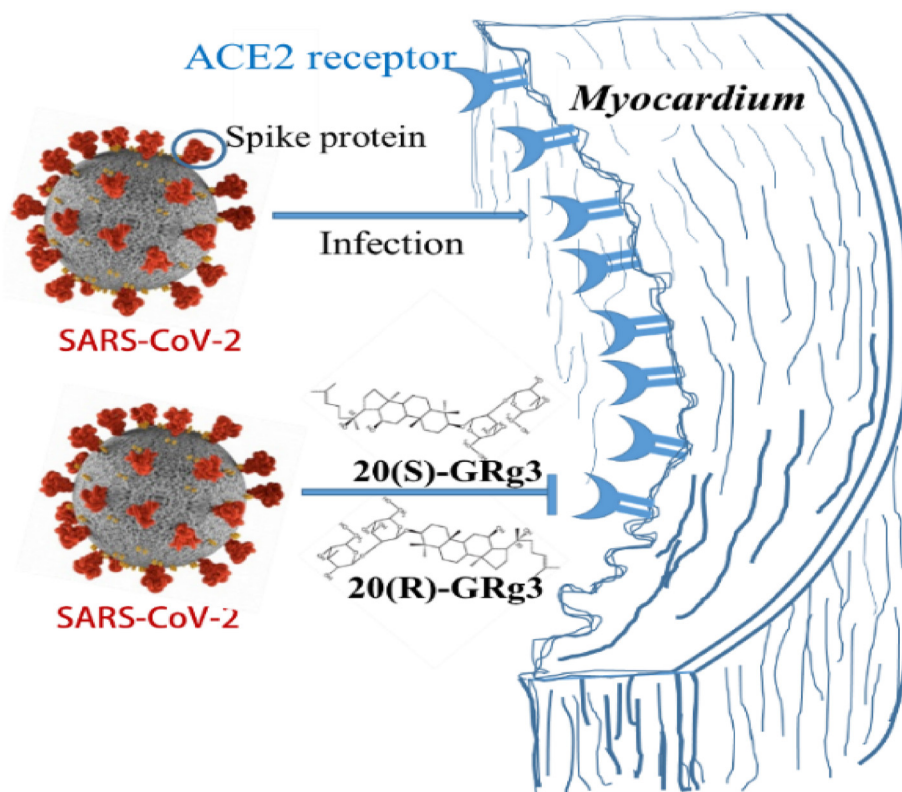
### 2.1. Cardiac injury with SARS-CoV-2 and ginseng/ginsenosides

#### 2.1.1. Ginsenosides on cardiac damage through ACE2 receptor with SARS-CoV-2

A recent study found that SARS-CoV-2 binds to angiotensin-conversion enzyme 2 receptor (ACE2), which is highly expressed in the heart and lungs, and infects the heart and lung tissue. In this regard, ACE2 expressed in the heart and lungs is an enzyme that plays a very important role in maintaining cardiovascular function normally. When infected with COVID-19, SARS-CoV-2 first binds to ACE2 present in the cell membrane, enters the cell, and abnormally changes the ACE2 signaling transduction, resulting in acute myocarditis and lung damage [18]. That is, normally ACE2 were expressed in the cell membranes of the heart and lungs, and receptor binding domain (RBD) of the SARS-CoV-2 spike glycoprotein binds to each other with ACE2 and enters the heart and lung tissue cells through interaction, thereby inhibiting the function of the ACE2 can block SARS-CoV-2 virus infection [19] (Fig. 3).



**Fig. 2.** A schematic diagram of cardiovascular complications caused by SARS-Cov-2. SARS-CoV-2 infection can cause various cardiovascular complications such as heart failure, myocarditis, myocardial infarction and many others.



**Fig. 3.** Schematic representation for the mechanism by which the SARS-CoV-2 invades the heart through binding with the angiotensin converting enzyme 2 receptor (ACE2) and by which 20(S)-ginsenosides Rg3 and 20(R)-ginsenoside Rg3 inhibited the invasion of SARS-CoV-2. SARS-CoV-2 can directly infect cardiomyocytes, attaching to ACE2 through its spike protein and entering the cell.

Ginsenosides are generally divided into three groups: protopanaxadiols, protopanaxatriols, and oleanane (ginsenoside Ro). Protopanaxadiols have sugar moieties on the C-3 position of dammarane-type triterpene, such as ginsenosides Rb1, Rb2, Rb3, Rc, Rd, Rg3, Rh2, and Rh3. Protopanaxatriols have sugar moieties on the C-6 position of dammarane-type triterpene, such as ginsenosides Rg1, Rg2, Re, Rf, and Rh1 [20–22]. In line with the above

observations, 20(S)-ginsenoside Rg3, the main active ingredient of panax ginseng, blocks RBD-ACE2 interaction through direct inhibition of RBD of the SARS-CoV-2 spike glycoprotein. That is, RBD of SARS-CoV-2 spike glycoproteins to cell membranes in the heart and lung tissue were blocked by 20(S)-ginsenoside Rg3 and 20(R)-ginsenoside Rg3 [19]. In addition, recent studies have shown that 20(S)-ginsenoside Rg3 and 20(R)-ginsenoside Rg3 effectively

inhibited viral infection of SARS-CoV-2-like lentivirus and SARS-CoV-2 virus in cells expressing receptors of human SARS-CoV-2 spike glycoprotein. These results indicate that 20(S)-ginsenoside Rg3 and 20(R)-ginsenoside Rg3, which are the main active ingredients of panax ginseng, directly inhibit the RBD of SARS-CoV-2 spike glycoproteins, ultimately preventing a viral infection. That is, treatment of 20(S)-ginsenosides Rg3 and 20(R)-ginsenoside Rg3 indicates the possibility that the risk of antiviral infection can be reduced by inhibiting the interconnection between the RBD of SARS-CoV-2 spike glycoproteins and ACE2 expressed in cardiomyocytes [19]. On the other hand, unlike immune antibodies, 20(S)-ginsenoside Rg3 and 20(R)-ginsenoside Rg3 effectively inhibit binding with ACE2 by targeting regions of receptors per SARS-CoV-2 spike, which are not accessible to biomolecules. These results indicate that 20(S)-ginsenoside Rg3 and 20(R)-ginsenoside Rg3 can inhibit intracellular invasion of SARS-CoV-2 to protect heart following SARS-CoV-2 infection. This suggests that 20(S)-ginsenoside Rg3 and 20(R)-ginsenoside Rg3 can effectively protect heart and lung tissue against SARS-CoV-2 infections, which are currently threatening human health worldwide.

### 2.1.2. Ginseng/ginsenosides on systemic inflammation with SARS-CoV-2

Inflammation is an immunological response to infection or injury and is associated with numerous human diseases [9]. Normal balance between inflammatory cytokines (TNF- $\alpha$  and IL-1) and anti-inflammatory cytokines (IL-2, IL-4, IL-10) *in vivo* is critical for *vivo* homeostasis, and imbalance between inflammatory cytokines and excessive production of such cytokines causes very serious inflammatory diseases [20,21]. COVID-19, which is currently spreading worldwide, causes acute systemic inflammatory reactions and cytokine storms, causing very serious damage. Especially, COVID-19 causes damage to the heart and lung tissues, leading to death. Many studies have shown that very high levels of inflammatory cytokines are produced in patients with COVID-19 [4,23] (Fig. 4).

On the other hand, through numerous previous studies, the anti-inflammatory effect of ginsenoside, an active ingredient of

ginseng, is widely known. In this regard, ginsenoside inhibited cytokine expression (TNF-, IL-1, IL-6), indicating anti-inflammatory action in macrophages, which are immune cells in the body [20,21]. Among them, the most widely known ginsenosides are Rb1, Rg1, Rg3, Re, Rd, and Rh1. Kim et al. suggested the role of ginsenosides in inflammatory responses and diseases [20]. Ginsenoside Rc is one of the main protopanaxadiol-based saponins isolated from ginseng. Such ginsenoside Rc represents anti-inflammatory action by inhibiting p38/ATF-2 signals and TANK-binding kinase 1/I $\kappa$ B kinase/interferon regulation factor-3. In addition, ginsenoside Rf inhibits the inflammatory mechanism in the p38/NF- $\kappa$ B-activated condition. That is, ginsenoside Rf significantly reduced the production of interleukin-1, interleukin-6, TNF- $\alpha$ , NO, and reactive oxygen species, which are inflammatory cytokines in HT-29 intestinal epithelial cells and macrophages [24]. In addition, anti-inflammatory activity of ginsenoside Rb1 and Rg1 were reported in previous studies. That is, the ginsenosides Rb1 and Rg1 exhibit anti-inflammatory effects by inhibiting antioxidant and NO synthesis [25,26]. In this regard, ginseng glycopeptide has been presented with anti-inflammatory efficacy in inflammatory pain models induced by animals [27]. Taken together, these results indicate the possibility of ginseng and ginsenosides-Rb1, Rg1, Rg3, Re, Rd, Rh1, Rc, and Rf capable of reducing the inflammation by SARS-CoV-2.

### 2.1.3. Ginseng/ginsenosides on coronary artery dysfunction with SARS-CoV-2

Among the blood vessels in the heart, arteries are often even coronary arteries. The heart serves as a pump that supplies oxygen and nutrients through blood in the body. To function as this pump, continuous oxygen and nutrients are required, and the heart coronary artery supplies blood to the muscle of the heart. In cardiac artery (coronary artery) plays a particularly important role in vascular homeostasis [28,29]. A recent study reported that vascular endothelial damage during SARS-CoV-2 has the most harmful effect in COVID-19 [30,31]. Such damage to vascular endothelial cells can be caused by both intravascular thrombosis and direct viral infection [32,33]. Among them, the mechanism of vascular damage caused by SARS-CoV-2 infection usually appears to be due to endothelial-mediated complications of COVID-19. In normal conditions, vascular endothelial properties exhibit anticoagulant and antithrombotic properties, and abnormal blood coagulation may occur through the generation of the von Willebrand factor (vWf), and the production of thromboxane and plasma activator inhibitor-1 (PAI-1) [34–36]. Vascular endothelial cell protects blood vessels through the expression of peroxide dismutase and glutathione that inhibit the progression of atherosclerosis [37,38]. On the other hand, when intravascular inflammation occurs, vascular endothelial cells are abnormally activated by inflammatory cytokines, resulting in local oxidation stress. These results cause disease in cardiovascular vessels, resulting in heart damage [39–41]. Recent studies have shown that vascular endothelial dysfunction is caused by SARS-CoV-2 infection. Hypoxia, hyperglycemia, inflammation and ischemia are also associated with SARS-CoV-2 [42–44]. That is, SARS-CoV-2 infection can cause very serious diseases such as vascular damage. In many recent studies, biomarkers of vascular damage indicators were identified in patients infected with SARS-CoV-2 [45–48]. As such, SARS-CoV-2 infection can be one of the very serious causes of vascular disease [49–52]. On the other hand, Korean Red Ginseng extract was found to significantly improve NO synthesis in animal experiments. Kim et al. reported that ginsenoside, an active ingredient of ginseng, inhibited free radical damage in blood vessels in the lung tissue and increased NO production of vascular endothelial cells to enhance vascular function [53]. In addition, ginsenoside (10  $\mu$ g/ml) to the aortic endothelial

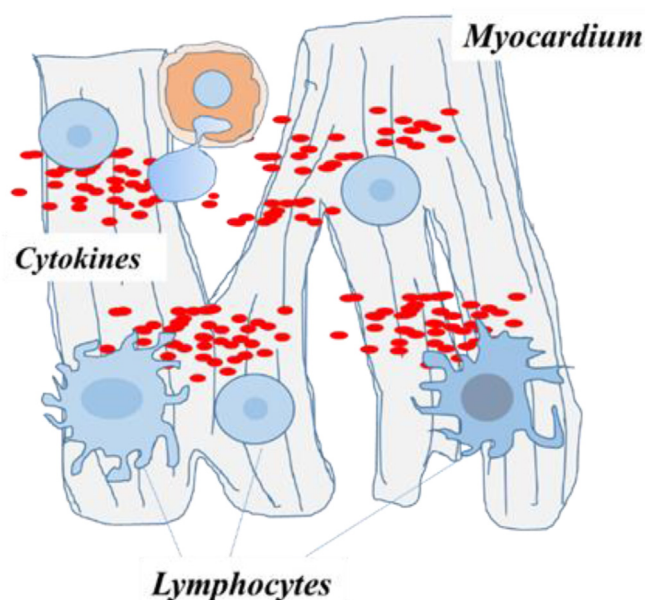


Fig. 4. SARS-CoV-2 can indirectly damage heart through systemic inflammatory responses and diminished blood supply (e.g., from blood clots and endothelitis, not shown).

cells significantly increases NO secretion that can protect vascular function by improving the  $\iota$ -Arginine signaling. In addition, it was well known that vascular function damaged by acetylcholine recovers normally when ginsenoside is treated. Also, other study reported also that the protophanaxatriol group among ginsenosides can improve vascular function through NO generation by improving the function of endothelial cells involved in NO production [54]. In another study, Korean Red Ginseng proved to have a relaxation effect of blood vessels through the generation of NO in brain tissue with dose-dependently [55]. In addition, Chan et al. proved that panax ginseng can improve vascular dysfunction by suppressing genes related to arteriosclerosis in diabetes complications [56]. In general, ginseng intake can improve vascular health from vasodilation and oxidative stress through anti-inflammatory cytokine control. In addition, it was found that ginseng has the effect of suppressing kidney failure by normalizing the vascular function of kidney tissue [57]. Consistent with the above observations, ginseng extract is known to inhibit lipid accumulation in cells and promote phosphorylation of PI3K/Akt/eNOS signaling pathways through overexpression of ET-1, thereby inhibiting endothelial cell damage due to hyperlipidemia [58]. In addition, ginsenoside Rb1 normalizes calcium metabolism *in vivo* and *in vitro* vascular smooth muscle cells. That is, ginsenoside Rb1 activates peroxisome proliferator active receptor (PPAR) and inhibits the Wnt/ $\beta$  $\gamma$  catenin pathway to normalize the signaling related to vascular function. And ginsenoside Rb1 restored vascular smooth muscle function by inhibiting  $\beta$  $\gamma$  catenin nuclear potential in vascular smooth muscle cells [59]. These results indicate that ginsenoside, an active ingredient in ginseng, has the effect of maintaining and restoring vascular function. Taken together, these results indicate the possibility of ginseng and ginsenosides capable of inhibiting the vascular dysfunction by SARSCoV-2.

## 2.2. Arrhythmias with SARS-CoV-2 and ginseng/ginsenosides

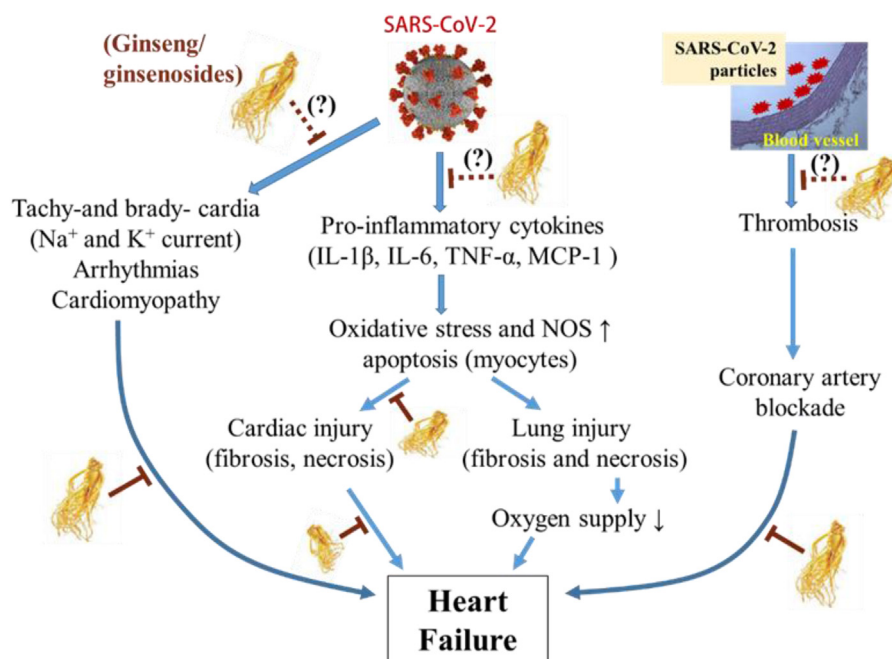
The heart function is performed by repetition of contraction and relaxation, but only when electrical stimulation is transmitted to heart muscle cells. Cardiac arrhythmia occurs if there is an abnormality in the generation or transmission of electrical signals in the heart, or if an abnormal electrical signal occurs. In other words, when arrhythmia occurs, regular contraction cannot continue, causing abnormal heartbeat. SARS-CoV-2, which is currently prevalent worldwide, has a very harmful effect on the heart. As a result, heart arrhythmia occurs, which can be a fatal risk [60,61]. According to a recent study, cardiac arrest and arrhythmia symptoms appeared in many of COVID-19 patients following SARS-CoV-2 infection [60]. Both tachycardia and arrhythmia occur during SARS-CoV-2 infection, and the incidence of arrhythmia in COVID-19 patients was reported to be 16.7%. Among patients with SARS-CoV-2, the rate of arrhythmia incidence was much higher when intensive care unit (ICU) hospitalization was required than when ICU hospitalization was not required [5]. On the other hand, antiarrhythmia drugs already used in clinical practice have side effects that worsen arrhythmia, so recently, they are attempting to develop antiarrhythmia drugs in natural herb without side effects. In this regard, ginseng is evaluated for anti-arrhythmia by normalizing K<sup>+</sup> current in guinea pig ventricular muscle cells. Also, ginsenoside Re was confirmed to have an effect of inhibiting arrhythmia electrophysiologically [62]. A recent study confirmed that ginsenoside is effective in treating cardiac arrhythmia by inhibiting cell membrane ion channels [63]. In many reports, ginsenosides are known to normalize the activity potential of cell membranes. That is, in the heart, L-type and T-type voltage dependent Ca<sup>2+</sup> channels that regulate the function of the heart exist in the myocardial cell membrane. Among them, the L-type Ca<sup>+</sup> channel is the main

channel of Ca<sup>2+</sup> required for heart cells to excite. Ginsenoside Rb1 is known to normally regulate Ca<sup>2+</sup> current on the guinea pig heart [64]. In addition, in another study rats with myocardial infarction, ginsenoside Rb1 played an effective role in normalizing heart function by regulating the flow of L-type Ca<sup>2+</sup> current and K<sup>+</sup> current [65]. In addition, ventricular arrhythmia was significantly improved when ginsenoside Re was administered in three doses (i.e., 5, 10, and 20 mg/kg) in the rabbit isoproterenol-induced arrhythmia model, thereby restoring heart function. In another study, ginseng saponin effectively prevented the occurrence of mouse ventricular arrhythmia with dose-dependently [66]. In particular, ginseng saponin was found to inhibit ventricular arrhythmia by normalizing Na<sup>+</sup> channel function in animal models with heart disease [67]. In addition, ginsenoside Re was found to have the effect of improving pathological arrhythmia by suppressing Na<sup>+</sup> and K<sup>+</sup> passages [68]. In other studies, total ginsenoside administration in mice with arrhythmia normalized the QRS complex, and increased T-wave amplitude resulted in decreased arrhythmia [69]. Also, it was reported that the co-administration of ginseng and digitalis may increase the arrhythmic effect [70]. Taken together, these results indicate the possibility of ginseng or ginsenosides capable of inhibiting the cardiac arrhythmias by SARSCoV-2.

## 2.3. Heart failure with SARS-CoV-2 and ginseng/ginsenosides

Heart failure refers to a disease by the cardiac functional abnormality to receive and pump blood, resulting in poor blood supply to the body. Acute heart failure during SARS-CoV-2 is a major symptom of COVID-19. Recent reports indicate that acute heart failure occurs in 23% of COVID-19 patients, and cardiomyopathy occurs in 33% of COVID-19 patients [71]. In present study, it was reported that heart failure has occurred in 24% of patients during SARS-CoV-2 infection, which is associated with an increased risk of death in COVID-19 patients [72]. Another study reported that SARS-CoV-2 causes various cardiovascular complications, including myocardial infarction, heart failure, and cardiac death [73]. It is known that heart failure occurs during SARS-CoV-2 infection, causing the heart to interfere with blood circulation efficiently in the body, but the exact pathogenesis is not known (Fig. 5).

Studies have shown that ginseng protects cardiac function in acute left ventricular failure animal models, which can help prevent heart failure [74]. Another study reported that panax ginseng helps prevent serious heart failure and maintain heart function. On treatment of ginseng, the mortality rate was significantly decreased and cardiac function was in heart failure [75]. Ginsenoside, an active ingredient of ginseng, is known to significantly suppress the occurrence of left and right ventricular hypertrophy and heart failure. Specifically, ginsenoside Rg1 maintained cardiac function by preventing heart failure in animals. The mechanism of inhibiting heart failure of ginsenoside Rg1 is associated with the normal regulation of ERK mitogen-activated protein kinase (MAPK) and Kalinin signaling [76]. In another study, oral administration of ginseng effectively decreased the occurrence of heart failure in animals and inhibited the hypertrophy of the left ventricle [77]. In addition, in animal experiments, ginsenoside Rb1 significantly inhibited right ventricular hypertrophy and consequently recovered heart function [78]. In another study, ginseng significantly suppressed heart failure by increasing the expression of PPAR in streptozotocin-induced diabetic animal model. Therefore, ginseng can be developed as a good treatment for heart failure without side effects [79]. Taken together, these results indicate the possibility of ginseng or ginsenosides capable of inhibiting the heart failure by SARSCoV-2.



**Fig. 5.** This schematic diagram illustrates the mechanisms of inhibition of ginseng by which COVID-19 induces heart failure. SARS-CoV-2 within the cardiomyocytes may cause infiltrative cardiomyopathy leading to heart failure. Moreover, pro-inflammatory cells release cytokines TNF- $\alpha$ , IL-1 $\beta$ , IL-6 and many others.

#### 2.4. Myocardial ischemia with SARS-CoV-2 and ginseng/ ginsenosides

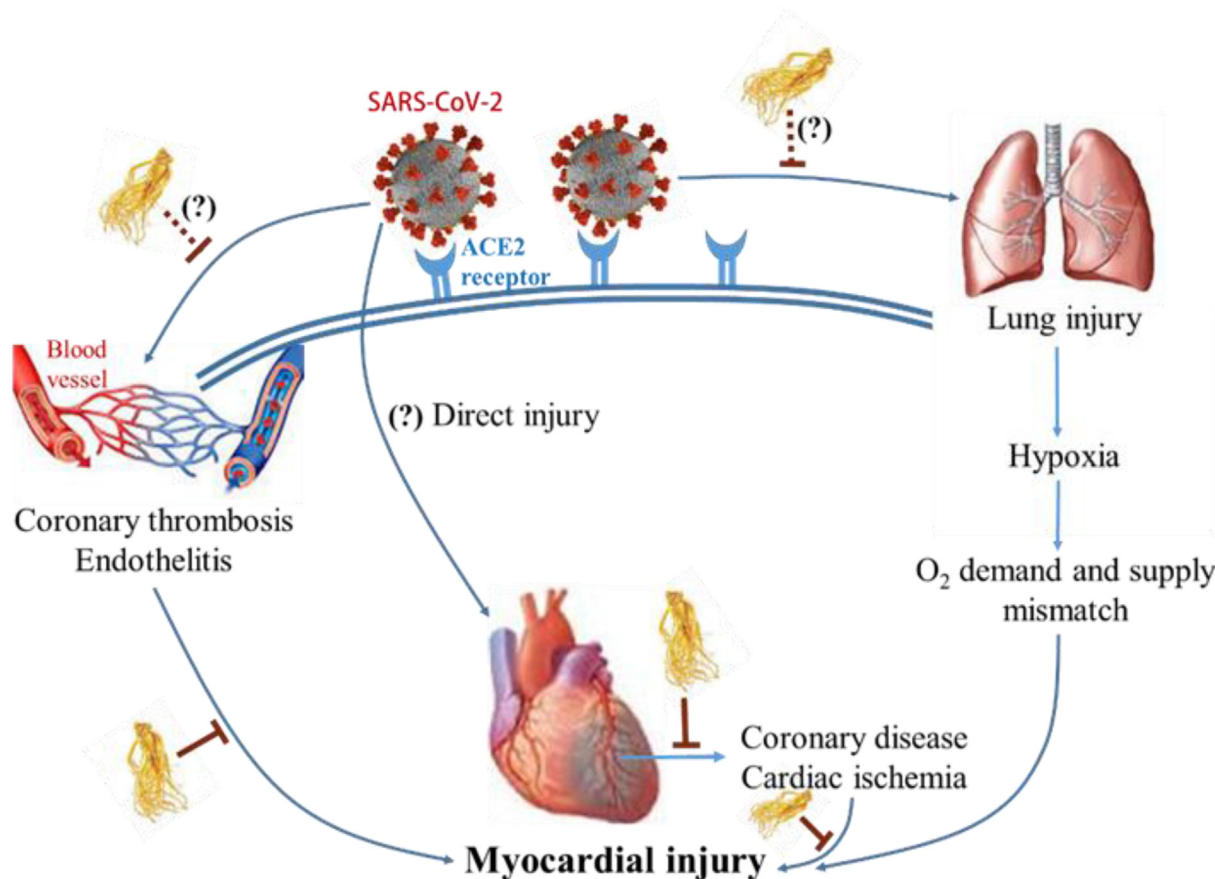
In human, the heart is operated by coronary arteries receiving oxygen and nutrients. If any of these coronary arteries are blocked by thrombosis, the supply of oxygen and nutrition is rapidly reduced, killing tissues or cells in the heart muscle. Such a disease is called myocardial infarction. Myocardial ischemia is very closely related to the occurrence of heart failure. Recently, human life-threatening SARS-CoV-2 is widespread, that causes a risk of acute respiratory syndrome due to severe respiratory infections. In addition, SARS-CoV-2 causes myocardial infarction and increases mortality [80]. In this regard, it is well known that COVID-19 is a risk factor for myocardial ischemia and stroke [81]. Patients infected with SARS, which occurred worldwide several years ago, caused myocardial damage, resulting in arrhythmia, cardiac dysfunction, and heart failure, leading to death [82]. Evidence that SARS-CoV-2, which is in vogue recently, causes myocardial damage is very well known. In a study by Chen et al. indicators of myocardial injury and inflammation were observed such as NT-proBNP, hs-CRP, and cTnI in COVID-19 patients, indicating that there was damage to the heart (Fig. 6).

Ginsenoside is known to protect the heart from doxorubicin-induced cardiac damage and suppress heart hypertrophy [83]. In other study, left ventricular hypertrophy was significantly suppressed when ginsenoside Rg1 was administered, and heart function was restored in animals [84]. In addition, ginsenoside Rb1 inhibited myocardial infarction in an ischemic and reperfusion injury, resulting in heart protection [85]. In addition, ginsenoside Rg1, an active ingredient of ginseng, was confirmed to reduce left ventricular hypertrophy. And Panax ginseng significantly inhibited apoptosis of cardiomyocytes by controlling Bcl-2 and Caspase-3 [86]. In another study, ginsenoside Rg1 protected cardiomyocytes from oxidative injury through antioxidant function [87]. And ginseng saponin, panaxadiol, and panaxatriol significantly protected the heart from experimentally induced ischemia and reperfusion damage [88]. Another study argued that ginseng

inhibits cardiac hypertrophy and heart failure [89]. Moreover, the ginsenoside Rb1 derivative, compound K, was shown to increase heart function by maintaining NO production through Akt/phosphoinositol 3-kinase (PI3K) pathway [90]. Taken together, these results indicate the possibility of ginseng or ginsenosides capable of inhibiting the myocardial injury by SARS-CoV-2.

#### 2.5. Vascular thromboembolic risk with SARS-CoV-2 and ginseng/ ginsenosides

It is known that COVID-19 patients significantly increase their risk of vascular thrombosis [91]. In particular, when a severe immune response such as a cytokine storm occurs, the synthesis of CRP or fibrinogen was increased due to overproduction of IL-6 in the liver, which increases thrombogenesis. Both abnormal coagulation and pathological diseases in the blood are potential factors that increase the risk of vascular thrombosis [92]. In a study of 25 patients with COVID-19 pneumonia, thrombosis were increased in 10 patients with pulmonary embolism. Infection with SARS-CoV-2 results in pulmonary embolism, with patients showing an increase in D-dimer levels [93]. In another study, the use of anticoagulants in severe COVID-19 infection is effective in reducing mortality, so prevention of thrombosis is considered very important in SARS-CoV-2 patients [94]. In this regard, ginseng is known to have a significant effect on preventing platelet aggregation. Korean Red Ginseng has an inhibitory action against platelet aggregation, and as a result, it plays an important role in preventing the occurrence of arterial thrombosis in the body. This suggests that red ginseng has a very beneficial effect on preventing cardiovascular disorders caused by thrombosis [95]. Another study reported that ginsenoside Rg3 inhibited the activity of AMP and extracellular signal regulation kinase 2, consequently inhibiting platelet aggregation via the inhibition of platelet aggregation signaling [96]. In another study, ginseng also significantly improved microcirculation disorder by preventing white blood cells from adhering to blood vessel and releasing various cytokines [97]. In addition, co-administered with Korean Red Ginseng and warfarin showed anti-coagulant



**Fig. 6.** Schematic diagram on possible pathophysiological mechanisms in COVID-19 infection and prevention of myocardial injury by ginseng. Abbreviations: ACE: angiotensin converting enzyme.

efficacy in patients [98]. And, total ginsenoside significantly increased coronary perfusion flow in cardiac ischemia and reperfusion injury. These results indicate that total ginsenosides have a protective action of heart tissue by normalizing the function of coronary artery. These results indicate that ginseng or ginsenoside has the action of suppressing a vascular injury caused by thrombosis. Taken together, these results indicate the possibility of ginseng or ginsenosides capable of inhibiting the vascular thrombosis by SARS-CoV-2. We summarized the effects of ginseng and ginsenosides on the protection of cardiovascular diseases such as myocardial ischemia, inflammation, heart failure, thrombosis, arrhythmia as follows. (Table 2).

### 3. Discussion

The COVID-19 pandemic, which currently has a fatal damage on human health worldwide, is bringing unprecedented challenges. COVID-19, which began in Wuhan, Hubei Province, China in 2019, is showing a global epidemic, and has sequentially spread beyond the pandemic in the world, resulting in many infections and deaths. Such COVID-19 causes harmful effects on the respiratory system, cardiovascular system, digestive system and many others. Such epidemics of COVID-19 presented a very high risk worldwide, but there is no effective treatment yet. Red ginseng, a traditional medicine, also has antiviral efficacy for a wide range of viral

**Table 2**  
Effects of ginseng and ginsenosides on protecting cardiac disorders.

Ginseng Ginsenoside	Myocardial/ischemia	Inflammation/heart failure	Vascular disease/Thrombosis	Arrhythmia
Panax ginseng (Total ginsenosides)	[88]	[74,75,79]	[53,55,56,98]	[69]
Ginsenoside Rg3	[19]	[19]		[96]
–20(S) and 20(R)				
Ginsenoside Rb1	[85]	[20]	[59]	[64,65]
Ginsenoside Rc		[20]		
Ginsenoside Re		[20]		[66,68]
Ginsenoside Rh2				
Ginsenoside Rg1	[84]	[25,26,76]		
Ginsenoside Rf		[24]		

diseases such as influenza virus, respiratory syncytial virus, rhinovirus, human immunodeficiency virus and herpes simplex virus, and so far, various animal and clinical studies have confirmed the antiviral efficacy of ginseng [99]. As such, traditional medicine has a long history in Asian countries such as Korea and China, contributes a lot to the prevention and treatment of severe infectious diseases, and its effectiveness has been proven. It was well known that studies have suggested the antiviral efficacy of ginseng and ginseng extracts. Therefore, if ginseng is conducive to COVID-19 or can protect the heart and lungs, it will be possible to improve the symptoms of COVID-19. However, there is still no direct evidence that natural products such as ginseng will be significantly effective for COVID-19 patients. In addition, there is no direct studies that ginseng and ginsenosides prevent cardiovascular side effects such as arrhythmia, myocardial infarction, heart failure, and vascular thrombosis in COVID-19 patients. However, the present review suggested that 20(S)-ginsenoside Rg3 and 20(R)-ginsenoside Rg3 effectively inhibited viral infections of SARS-CoV-2-like lentiviruses and SARS-CoV-2 viruses in cells expressing receptors of human SARS-CoV-2 spike glycoproteins [19]. And, it was suggested that ginsenoside Rf inhibited the inflammatory mechanism related to the p38/NF- $\kappa$ B-signaling and significantly reduced the production of interleukin-1, interleukin-6, TNF- $\alpha$ , NO, and free radicals [24]. In addition, it was presented that ginsenosides Rb1 and Rg1 exhibit anti-inflammatory effects by inhibiting antioxidant and NO synthesis [25,26]. In addition, red ginseng significantly enhances NO synthesis and secretion of vascular endothelial cells, which is the result of increased NO production by suppressing free radical damage in blood vessels [53]. And, Korean Red Ginseng has vascular relaxation effect through the production of NO [55], and that panax ginseng suppresses genes related to arteriosclerosis, thereby improving vascular dysfunction [56]. Also, ginseng saponin effectively prevents ventricular arrhythmia [66], and ginsenoside Re showed the effect of improving pathological arrhythmia in animal models [68]. Furthermore, the treatment of Panax ginseng decreased severe heart failure and mortality, and heart function was significantly improved by the protection of heart failure in ginseng-treated group. The present review suggested that ginsenoside protected myocardial cells from oxidative injury, and ginseng saponin significantly protected the heart from ischemia and reperfusion damage. Also, the administration of ginseng in animal has the effect of inhibiting heart hypertrophy and heart failure. Therefore, this review will be an opportunity for ginseng and ginsenoside to suggest a possibility for an applicability of adjuvant therapy to COVID-19 patients in the future. However, importantly, in order to use ginseng and ginsenosides for COVID-19 patients, it is judged that many scientific studies must be accumulated in the future.

### Declaration of competing interest

The authors have declared no conflict of interest.

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