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Review Article

Effects of *Panax* ginseng and ginsenosides on oxidative stress and cardiovascular diseases: pharmacological and therapeutic roles

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ABSTRACT

Traditionally, Asian ginseng or Korean ginseng, *Panax* ginseng has long been used in Korea and China to treat various diseases. The main active components of *Panax* ginseng is ginsenoside, which is known to have various pharmacological treatment effects such as antioxidant, vascular easing, anti-allergic, anti-inflammatory, anti-diabetes, and anticancer. Most reactive oxygen species (ROS) cause chronic diseases such as myocardial symptoms and cause fatal oxidative damage to cell membrane lipids and proteins. Therefore, many studies that inhibit the production of oxidative stress have been conducted in various fields of physiology, pathophysiology, medicine and health, and disease. Recently, ginseng or ginsenosides have been known to act as antioxidants in vitro and in vivo results, which have a beneficial effect on preventing cardiovascular disease. The current review aims to provide mechanisms and inform precious information on the effects of ginseng and ginsenosides on the prevention of oxidative stress and cardiovascular disease in animals and clinical trials.

1. Introduction

The body is constantly exposed to various forms of free oxygen, for example reactive oxygen species. Oxidative stress can be defined as a state in which oxidative mechanisms prevail against antioxidant defense mechanisms in living cells, causing oxidative damage to cell proteins, lipids, and nucleic acids. Oxidative stress is caused by free radicals, which are oxygen ions, free radicals, peroxides, etc. Free radicals are produced and accumulated in the cell transport system and are also produced by ionizing radiation. In humans, oxidative stress is believed to be an important development mechanism in smoking [1,2], high blood pressure [3,4], atherosclerosis [5–8], hyperlipidemia [9], diabetes [10], ischemia-reperfusion, cancer [11], rheumatoid arthritis [12], aging [13–15]. Cardiovascular diseases (CVD) are a very serious problem worldwide and are closely related to blood flow disorders. CVD, in particular, includes a variety of diseases such as coronary artery disease, heart failure, vascular disease, dyslipidemia, and high blood pressure, causing serious health problems for many people worldwide and leading causes of disease and mortality. These cardiovascular diseases occur especially in adults exposed to westernized diets, which have a fatal effect on people of all races. In this regard, cardiac risk factors such as oxidative stress, diabetes, high blood pressure, increased low-density cholesterol, and reduced high-density cholesterol levels are known as major causes of CVD [16]. In many studies, damage to endothelial cells in blood vessels can be a factor associated with cardiovascular disease [17].

Panax ginseng Meyer, with a history of thousands of years, is a medicinal herb that has traditionally been effective in preventing and treating many diseases. Especially in Korea, China, and Japan, ginseng has been known as the most effective natural product of all herbs, and has traditionally been widely used to replenish physical strength, and prevent aging [18]. It is also known that ginsenosides increase resistance to a variety of pathological factors, while helping to maintain body homeostasis. Of the ginseng ingredients, more than 100 ginsenosides have been identified so far, and various pharmacological validations are included. In addition, ginseng, and ginsenoside are known to be effective in improving blood flow and protecting cardiovascular dysfunction. In other words, numerous studies on blood flow and cardiovascular function have shown that ginseng and ginsenosides have a valid effect on cardiovascular

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protection. The main active ingredient of *Panax* ginseng is ginsenoside, a triterpen saponin. Among them, many studies have been mainly conducted on the pharmacological and clinical properties for ginsenosides [19]. Here, the present review aims to provide an overview of the efficacy of ginseng and ginsenosides against oxidative stress and cardiovascular risk factors such as vascular inflammation, endothelial dysfunctions hypertension, atherosclerosis and myocardial infarction in clinical studies as well as *in vivo* in order to induce the pharmacological and clinical applications.

1.1. Ginsenosides are the pharmacologically active components

Ginseng contains many active ingredients that represent function in vivo, of which ginsenosides are very important. About 200 ginsenosides are known, including major ginsenosides (Rc, Rd, Rb1, Rb2, Re, Rg1, etc.) and minor ginsenosides (Rh1, Rh2, Rg3, etc.) [20]. Ginsenosides are classified into two major groups, protopanaxadiol (PD) and protopanaxatriol (PT), which share a four-ring hydrophobic steroid-like structure with sugar moieties but differ in the carbohydrate moieties at C3, C6, and C20 (Fig. 1) [21,22]. So far, ginsenosides are largely divided into two types: (1) 20(S)-Protopanaxadiol (PD) (ginsenoside-Rb1, Rb2, Rb3, Rg3, Rh2, Rc, Rd, Rs1) and (2) 20(S)-Protopanaxatriol (PT). These ginsenosides are known to have more than 30 species. (Fig. 1)

According to the manufacturing processing method of ginseng, *Panax* ginseng is divided into three types: fresh ginseng, Korean Red Ginseng (KRG), and white ginseng. Until now, red ginseng is manufactured in Korea, so it has been named KRG. KRG generally was cooked by steaming and drying. White ginseng is dried without cooking by sunlight or hot air; white ginseng's color ranges from white to light yellow [23,24]. In particular, KRG undergoes component conversion during the heat process, producing novel components (e.g. ginsenosides-Rg2, -Rg3, and -Rh1) that are not contained in fresh ginseng and white ginseng [25–30].

1.2. Oxidative stress and cardiovascular disease

It was well known that oxidative stress is a state of unbalance between oxidants and antioxidants, leading to damaging normal condition [31]. Oxidants, called the reactive oxygen species (ROS), contains free radicals such as $OH^{\bullet}$ (hydroxyl), $O^{2\bullet-}$ (superoxide), $ONOO^{\bullet-}$ (peroxynitrite), and non-radicals such as hydrogen peroxide (H_2O_2). ROS are the output of aerobic metabolism by reduction of oxygen [32,33]. Physiologically, in human, antioxidant systems are capable of controlling the levels of oxidants in order to keep the oxidant-antioxidant equilibrium [31,34]. This antioxidant system includes enzymes such as catalase, superoxide dismutase, and glutathione peroxidase, [35]. Recent studies have suggested that the increases of reactive oxygen species (ROS) and oxygen utilization contribute to CVD outbreak. A representative listing for oxidative mechanisms is shown in Table 1.

1.3. The effect of ginseng or ginsenosides on oxidative stress

It was well known that ginseng and ginsenosides have a function of the antioxidant activities. Namely, when ginsenoside-Rb1 was administered to animals, lipid peroxidation in the brain was reduced, oxygen free radicals were removed, and the catalase, and glutathione peroxidase activities increased [47]. Also, taking a different approach, treatment of ginsenoside for three days prevented the lipid peroxidation of liver and brain in rat. Moreover, ginsenoside-Rb1 was found to remove free radicals, inhibit the formation of malondialdehyde (MDA), and increase CAT and GPx activity in the liver [48]. In addition, intraperitoneal injection of ginseng total saponin (TS) into mice for five days resulted in a significant reduction in free radical and MDA [49]. In addition, GPX activity increased when oral administration of water extracts, fat-soluble extracts, alcohol extracts, total saponin extracts, protopanaxadiol (PD) extracts, and protopanaxatriol (PT) extracts to mice aged 4 weeks, respectively, showing significant antioxidant effects [50]. These results presented that ginsenosides have an antioxidant role, inhibiting oxidative damage, and that these protective action of ginsenosides can be chiefly attributed to scavenging of ROS.

1.4. The effect of ginseng and ginsenosides on myocardial damage

Ginseng is widely used to address heart failure, cardiovascular risk diseases, high blood pressure, and hypercholesterolemia [51–54]. The administration of ginseng significantly increases the level of antioxidant enzymes such as peroxidase and glutathione peroxidase through Nrf2 regulatory mechanism [55]. The presence of heart ischemia increases free oxygen production, which is caused by myocardial damage, but administration of ginseng improves cardiac coronary blood flow, reducing free oxygen production, inhibiting myocardial damage [56]. Ginseng inhibits the production of free radicals by promoting nitrogen oxide production. The administration of ginsenoside-Rb1 blocked vascular endothelial dysfunction caused by homocysteine by inhibiting the production of free oxygen species [57]. In another study, ginsenoside-Re played a role in inhibiting the production of free oxygen species and protecting them from oxidative damage to myocardial cells. And ginsenoside-Re played an important role in the antioxidant effect of increasing the viability of myocardial cells in heart ischemia [58]. These results show that ginsenoside-Re has an antioxidant effect that protects the heart cells from oxidative damage, and most of them have significant effects on the removal of free radicals. These

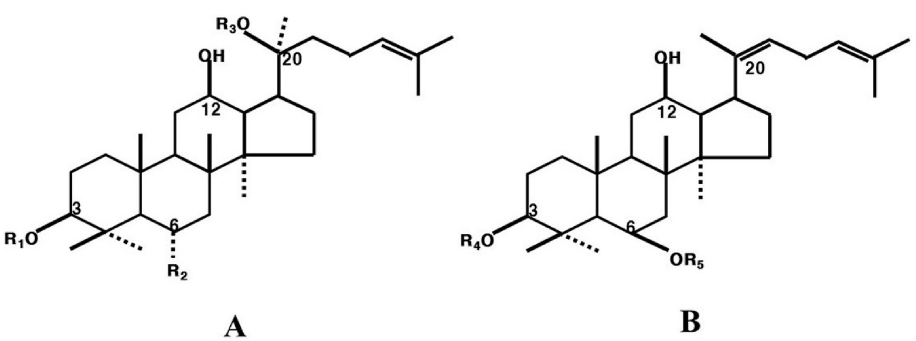

Fig. 1. Molecular structures of protopanaxadiol (A) and protopanaxatriol (B) of ginsenosides.

Table 1
Representative evidence of ROS production in CVD

Condition	Evidence	Reference
Heart failure	Increased NO level induces cardiac dysfunction	[36]
	Cytokine-derived ROS induces cardiac apoptosis	[37]
	ROS-induced cardiac apoptosis or necrosis	[38]
Hypertension	Vascular smooth muscle cell proliferation	[39,40]
	Increases oxidant production via NADH/NADPH oxidase	[41]
	Superoxide-mediated endothelial dysfunction	[42]
Coronary artery disease	Superoxide-mediated endothelial dysfunction	[43]
MI	Increased oxLDL	[44]
	Ischemia and reperfusion injury by ROS production	[45]
	Oxidant-induced myocyte necrosis and apoptosis	[46]

studies strongly suggest that ginseng or ginsenosides protect myocardial damage by inhibiting ROS generation.

1.5. The effect of ginseng or ginsenosides on vascular function

The administration of KRG water extract (KRGE) protected human umbilical vein endothelial cells. In other words, KRGE significantly promoted angiogenesis through PI3K/Akt-dependent ERK1/2 and eNOS signaling pathway activation [59]. Specifically, administration of KRGE induced angiogenesis through activation of PI3K/Akt-dependent extracellular signaling regulatory kinase 1/2 and eNOS pathways [59]. In vitro, *Panax* ginseng and *Panax* notoginseng extracts increased vascular endothelial cell proliferation and migration [60]. Additionally, administration of ginsenoside Rg3 significantly increased NO production through phosphorylation and eNOS expression, thereby enhancing vascular function [61]. Ginsenoside increased the production of nitrogen oxides. In other words, ginsenoside-Rb1 in aortic endothelial cells increased nitrogen oxide production through various mechanisms [62]. Similarly, ginsenoside-Rg3 induced vasodilation to improve arterial elasticity, thereby improving vascular function [63]. These results prove that ginseng or ginsenosides protect endothelial cells through various types of cell signaling pathways.

1.6. The effect of ginseng and ginsenosides on blood pressure

Many studies have shown that administration of ginsenoside-Rb3 and KRG improves vascular dysfunction [64,65]. In addition, administration of KRGE inhibited arginase and showed vascular protection through increased NO production [66]. In addition, ginseng improved low blood pressure in previous studies, maintaining normal blood pressure through the production of nitrous oxide secreted from endothelial blood vessels [67]. In other studies, total ginsenosides significantly increased ventricular systolic pressure and ventricular hypertrophy. Total ginsenosides also significantly improved cardiac function by controlling the expression of extracellular signaling regulatory kinase 1 (ERK-1) and mitogen-activated proteins. Namely, total ginsenosides is effective in protecting against right ventricular hypertrophy and can lower pulmonary hypertension. Such effect has been shown to involve several molecular mechanisms, such as inhibition of ERK signaling pathways [68]. These results show that total ginsenosides can improve vascular motor function.

1.7. The effect of ginseng and ginsenosides on cardiac function

Ginsenoside-Rg1 protected against left ventricular hypertrophy by producing nitrogen oxides [69]. Ginsenoside-Rb1 also significantly inhibited heart damage from ischemia-induced myocardial infarction in type 1 diabetic animal models induced by STZ [70]. Ginsenoside-Rg1 also reduced left ventricular hypertrophy, and inhibited the cell death of myocardial cells by inhibiting the expression of Bcl-2 and Caspase-3 during myocardial infarction caused by ischemia [71]. In another study, experiments were conducted on cultured neonatal ventricular muscle cells, as well as adult mice that bound the coronary arteries. The administration of ginseng significantly restored heart function in rats undergoing coronary artery ligation for four weeks. These results show strong heart protection effects of ginseng [72]. The administration of compound K significantly inhibited the magnitude of myocardial infarction resulting from ischemia compared to controls, significantly enhancing protein kinase B (Akt) and nitrogen oxide synthase (eNOS) activity. This indicates that compound K inhibits myocardial infarction following ischemia by mediating activation and phosphorylation of PI3K pathways in Akt and eNOS [73]. Previous studies have shown that ginsenoside-Rb1 inhibits cardiac dysfunction in diabetes caused by streptozotocin [70]. In other study, it was reported that ginseng inhibited heart failure and cardiac hypertrophy through Nhe-1 regulation and reduced the activation of calcium [74]. These results suggested that ginseng or ginsenosides maintain cardiac function.

1.8. The effect of ginseng and ginsenosides on vascular dysfunction

In the past few decades, a large amount of research studies have highlighted the significance of ginseng for preventing platelet aggregation. Korean Red Ginseng was found to improve arterial thrombosis in vivo, by causing inhibition of platelet aggregation rather than anticoagulation thus suggesting that red ginseng treatment can prove beneficial for cardiac dysfunction [75]. In another study, different ginsenosides-Rs3, -Rs4, -Rs5, -Rg6, -F4, -Rk3, -Rh4 extracted from processed ginseng were evaluated for platelet aggregation induced by stimulators viz-adenosine diphosphate, collagen, and arachidonic acid in which all ginsenosides except -Rs3, -Rs4, and -Rs5 had minor effect on aggregation. Also, co-administration of Korean Red Ginseng and warfarin was found to have synergistic benefits in patients with cardiac valve replacement [76]. In addition, administration of total ginsenosides in ischemic and reperfusion injury of isolated rat hearts resulted in coronary perfusion flow, thereby protecting the heart tissues by coronary artery dilation from I/R injury. Based on these results, it can be concluded that in vivo ginseng or ginsenosides possess antithrombotic effect inside the body that would be beneficial for individuals with thrombotic problems and CVD.

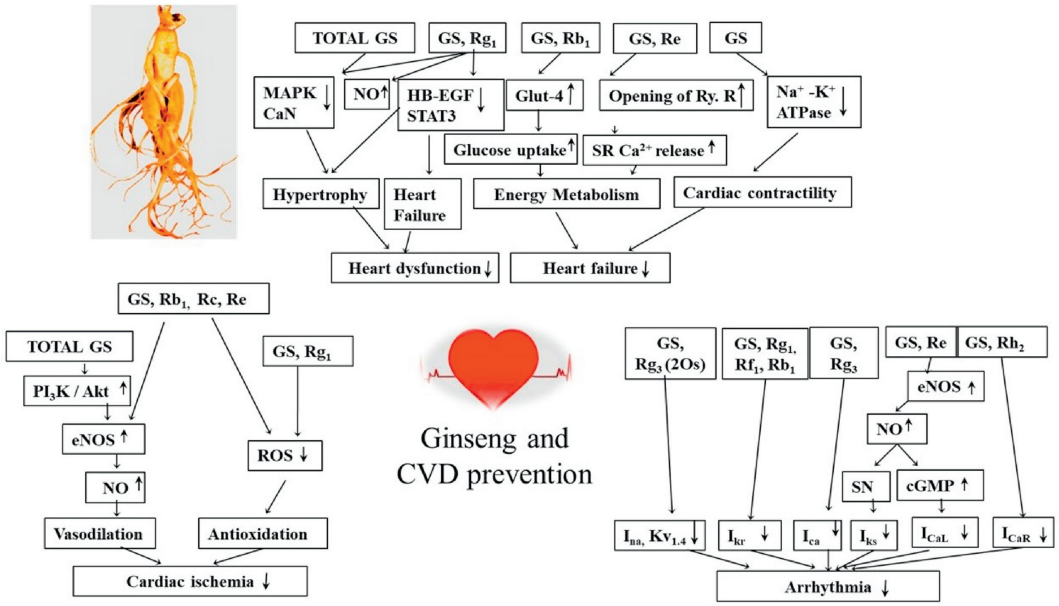

Fig. 2. Mechanisms of Ginseng in Protecting Heart. Notes: eNOS: endothelial nitric oxide synthase, GLUT-4: glucose transporter-4, GS: ginseng total saponins, HB-EGF: heparin-binding EGF-like growth factor, ICa,R: R-type calcium channel current, ICa,L: L-type calcium channel current, IKr: rapidly activating component of rectifier K+ current, MAPK: mitogen activated protein kinase, IKs: slowly activating component, PI3K/Akt: phosphoinositide 3-kinase/protein kinase B, RyRs: ryanodine receptors, ROS: reactive oxygen species, SR: sarcoplasmic reticulum, STAT3: signal transducer and activator of transcription 3, SN: S-nitrosylation of channel protein.

1.9. The effect of ginseng and ginsenosides on cardiac ischemia

It was well known that treatment with ginseng improved electrocardiogram, general symptoms, physical exercise capacity, and fluid metabolism in patients with coronary angina pectoris [77]. Cardio-protective effects of ginseng is attributed to its anti-oxidant properties in cardiomyocytes [78]. Amongst ginsenosides, panaxatriol has been found to most potent for providing protection against myocardial ischemia and reperfusion [72]. Total ginsenosides increased perfusion flow of the coronary artery dose-dependently. The underlying mechanism of vasodilatory activity seemed to be mediated by the phosphoinositide 3-kinase/protein kinase B-endothelial nitric oxide pathway that ultimately increase nitric oxide levels [79]. Accordingly, vasodilatory effect of total ginsenosides was decreased by an inhibitor of NO synthase. Ginsenoside-Rb1 treatment established the vasodilating mechanism of porcine coronary arteries by accentuating the regulation of NO synthase and down-regulation of superoxidases [57]. Ginsenoside-Rb1, ginsenosides Rc and Re successfully prevented HIV protease inhibitor mediated vascular injury in porcine coronary arteries on account of its vasodilatory effect through regulation of NO and superoxidase levels [80]. Thus, ginseng and ginsenosides can be believed to have multitude of beneficial effect on oxidative stress and cardioprotection. (Fig. 2).

1.10. Summary

In conclusion, present review suggested the antioxidant effect and cardiovascular protection of ginseng and ginsenosides. Also, review explained the antioxidants of ginseng, cardiac strengthening, vascular function improvement, blood pressure maintenance, improvement of cardiac function, inhibition of vascular damage and myocardial infarction. Significant review on the efficacy of ginseng and ginsenosides on cardiovascular risk factors such as heart ischemia is summarized. Ginseng and ginsenosides are effective in preventing cardiovascular disease. As shown above, ginseng and ginsenosides have a significant effects on CVD through inhibition of ROS formation, stimulation of NO production, strengthening vascular motor tone, and improving blood circulation. However, the exact mechanism of action of ginseng and ginsenosides has not been confirmed, and further research should reveal the various effects of ginseng and ginsenosides. Therefore, more systematic mechanisms for cardiovascular disorders through antioxidant action of ginseng and ginsenosides should be identified in the future. In addition, in order to develop ginseng and ginsenoside as natural medicines and use them, it is necessary to verify their efficacy and safety.

Declaration of competing interest

The authors declare no conflict of interest.

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