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Review article

Pharmacological and medical applications of *Panax ginseng* and ginsenosides: a review for use in cardiovascular diseases

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ABSTRACT

Panax ginseng, also called Asian or Korean ginseng, has long been traditionally used in Korea and China to treat various diseases. The major active ingredients of *P. ginseng* are ginsenosides, which have been shown to have a variety of therapeutic effects, including antioxidation, anti-inflammatory, vaso-relaxation, antiallergic, antidiabetic, and anticancer. To date, approximately 40 ginsenoside components have been reported. Current research is concentrating on using a single ginseng compound, one of the ginsenosides, instead of the total ginseng compounds, to determine the mechanisms of ginseng and ginsenosides. Recent *in vitro* and *in vivo* results show that ginseng has beneficial effects on cardiac and vascular diseases through efficacy, including antioxidation, control of vasomotor function, modulation of ion channels and signal transduction, improvement of lipid profiles, adjustment of blood pressure, improvement in cardiac function, and reduction in platelet adhesion. This review aims to provide valuable information on the traditional uses of ginseng and ginsenosides, their therapeutic applications in animal models and humans, and the pharmacological action of ginseng and ginsenosides.

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1. Introduction

Panax ginseng is one of the most commonly greatly used species of ginseng. For thousands of years, this species, which is native to Korea, China, and Japan, has been an important cure in traditional medicine, where it has been used mainly as a remedy for spiritlessness and fatigue [1]. The name *panax* means “all healing” and stemmed from the traditional confidence that ginseng can cure all illness of the human body. The main active components in *P. ginseng* are ginsenosides, which are triterpene saponins. Most research on the pharmacological and medicinal functions of *P. ginseng* has focused on ginsenosides [2]. Among the ginseng species, *P. ginseng* (Korean ginseng), *Panax notoginseng* (Chinese ginseng), *Panax japonicum* (Japan ginseng), and *Panax quinquefolius* (American ginseng) are the most common. A lot of research has focused on individual ginsenosides instead of whole ginseng against many disease conditions [3–8]; among these ginsenosides, Rb₁, Rg₁, Rg₃, Re, and Rd are most often studied [8]. Cardiovascular disease is the major cause of morbidity and mortality and includes various diseases such as vascular disease, heart failure, coronary artery disease, cardiac ischemia, and hypertension [9]. Cardiac risk factors, such as cigarette smoking, increased low-density

lipoprotein cholesterol, decreased level of high-density lipoprotein cholesterol, diabetes, and hypertension, are the main causes of cardiovascular disease [10]. Many researchers have shown that inflammation of blood vessels can result in atherosclerosis and coronary artery dysfunction [11]. Endothelial injury of blood vessels can be initiated by dangerous factors involved in cardiovascular disease [12]. Inflammation within the arterial wall is established by many cytokines, interleukins, and free radicals such as reactive oxygen species (ROS). Here, we review many research results on the roles and mechanisms of ginseng and ginsenosides to induce more studies into applications of ginseng and ginsenosides. The present review concentrated primarily on *P. ginseng*, but also considered studies on ginseng and ginsenosides

2. Ginsenosides are the pharmacologically active components in ginseng

Ginseng contains many active constituents, of which ginsenosides are very important. About 200 ginsenosides have been reported, including major ginsenosides (Rb₁, Rb₂, Rc, Rd, Re, Rg₁, etc.) and minor ginsenosides (Rg₃, Rh₁, Rh₂, etc.) [13]. By chemical structure, ginsenosides are classified into two major groups,

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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) [14,15]. To date, over 30 ginsenosides have been reported and classified into the two categories: (1) the 20(S)-PD (ginsenosides Rb₁, Rb₂, Rb₃, Rg₃, Rh₂, Rc, Rd, and Rs₁) and (2) the 20(S)-PT (ginsenosides Rg₁, Rg₂, Rh₁, Re, and Rf). The difference between PD and PT groups is the presence of a carboxyl group at the C6 position of PD [13,16].

Red ginseng, which results from the special preparation of ginseng, has an unusual saponin profile, with ginsenosides Ra₁, Ra₂, Ra₃, Rf₂, Rg₄, Rg₅, Rg₆, Rk₁, Rs₁, and Rs₂ likely being the results of stem transformation and deglycosylation of naturally generated ginsenosides [17–22]. These compounds can confirm the traditional knowledge that red ginseng is of higher pharmacological and medicinal functions than white ginseng [23]. Intestinal flora conditions change the relative composition of ginsenosides. Novel active compounds of ginseng formed by intestinal bacteria, such as compound K, might show more useful pharmacological and medical activities.

3. Ginsenosides modulate various ion channels

It was reported that ginsenoside Rd reversed the increase in store-operated Ca²⁺ channels or receptor-operated Ca²⁺ channels, but not voltage-dependent Ca²⁺ entry via a Ca²⁺ channel. This result suggests diminution of hypertensive remodeling after ginsenoside Rd administration [24]. Ginsenoside Re was shown to decrease heart rate, shorten the plateau phase of action potentials, and decrease P-wave amplitude, indicating blockade of slow Ca²⁺ channels mainly in the atria [25]. It was reported that ginseng depressed the L-type Ca²⁺ current in ventricular myocytes of guinea pig, and ginsenoside Re showed similar but weaker effects involving NO and the cyclic guanosine monophosphate pathway [26,27]. Ginsenoside Rg₃ decreased five subtypes of Ca²⁺ channel; L-, N-, P-, R-, and T-types [28,29]. Also, other ginsenosides have been shown to inhibit Ca²⁺ channels. For example, ginsenoside Rh₂ had a powerful inhibitory effect on L- and R-type Ca²⁺ channels, whereas compound K (CK) strongly blocked only the T-type Ca²⁺ channel [28]. Ginseng treatment delayed K⁺ current in ventricular myocytes of guinea pig, and ginsenoside Re demonstrated similar electrophysiological effects [26]. One study showed that NO induced by ginsenoside Re modulated cardiac K⁺ channel activation and protected against ischemia-reperfusion injury in the heart [30].

4. Ginsenosides modulate cellular signal transduction

Although ginseng and ginsenosides have been widely used as pharmacological and medical substances, only a few studies have

shown their effects on signal transduction pathways [31,32]. Ginsenoside Rg₁ can inhibit the C-Jun N-terminal kinase (JNK) signaling cascade through a protective effect against the phosphorylation of JNK [33]. In human astroglial cells, ginsenoside Rh₂ and compound K showed a primary inhibitory action on TNF- α -induced expression of adhesion molecule-1 by inhibiting TNF- α -induced phosphorylation of I κ B α kinase [34]. Also, ginsenoside Rh₂ and compound K inhibited the phosphorylation and degradation of I κ B α [34]. Furthermore, the same treatment with ginsenoside Rh₂ and compound K inhibited TNF- α -induced phosphorylation of MKK4 and suppressed the activation of the JNK-AP1 pathway.

5. Ginseng and ginsenosides improve antioxidant and blood circulation

Ginseng has antioxidative, vasorelaxation, anti-inflammatory, and anticancer activities [35]. In addition, ginseng is also widely used to address cardiovascular risk factors such as hypertension and hypercholesterolemia. Cardiac ischemia can be induced by myocardial damage through the production of ROS; however, ginseng and ginsenosides have been shown to improve the coronary blood flow [36]. In addition, an antioxidant role through Nrf2 and levels of antioxidant enzymes such as glutathione peroxidase and superoxide dismutase are increased by ginseng [37,38]. Ginsenosides inhibited myocardial injury through the increment of 6-keto-prostaglandin F_{1 α} and decreases of lipid peroxidation [39]. In addition, ginseng prevented ROS production through the stimulation of nitric oxide. Ginsenoside-Rb₁ and other ginsenosides blocked endothelial dysfunction induced by homocysteine through the inhibition of ROS production [40,41]. Ginsenoside Re is a strong antioxidant that conserves cardiomyocytes against oxidation via its free radical scavenging properties. Also, ginsenoside Re might play a primary role in an antioxidative effect to increase cardiomyocyte survival and cardiac contraction under cardiac ischemia [42,43]. These results suggest that ginsenoside Re has an antioxidant action, protecting cardiac cells from oxidative damage, and that these protective effects can be mostly attributed to scavenging of free radicals.

6. Ginsenosides ameliorate vascular function

It was well known that ginsenoside Rb₁ shows protective role on human umbilical vein endothelial cells [44]. Also, in such cells, a water extract of Korean ginseng induced angiogenesis through activation of phosphoinositol-3-kinase (PI3K)/Akt-dependent extracellular signal-regulated kinase 1/2 and endothelial nitric oxide synthase (eNOS) pathways [45]. Ginsenoside Re induced the activation of potassium channels in vascular smooth muscle cells [46]. *In vitro* extracts of *P. ginseng* and *P. notoginseng* increased

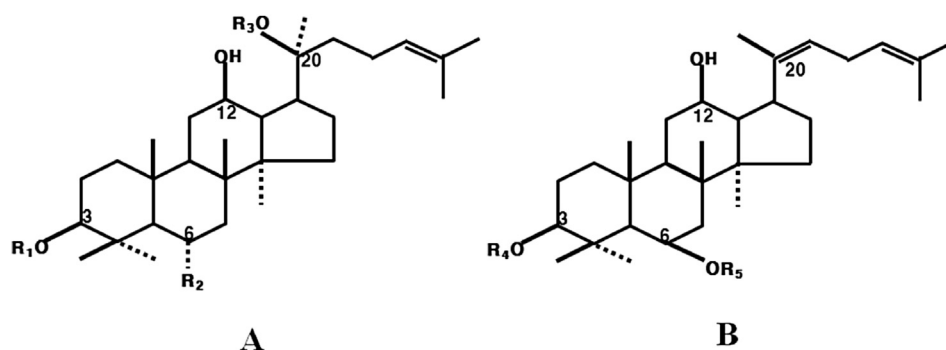


Fig. 1. Molecular structures of protopanaxadiol and protopanaxatriol of ginsenosides.

vascular endothelial cell proliferation and migration [47]. It has been also reported that ginseng reduced atherosclerotic lesions in mice [48], and that ginsenoside Rg₃ increased NO production through phosphorylation and expression of eNOS [49]. These studies suggest that ginsenosides protect vascular endothelial cells through the signaling pathways. Namely, ginsenosides regulate blood vessel tone through production and release of nitric oxide in the endothelium [50,51]. Nitric oxide production has been induced by ginsenosides through various mechanisms. Especially, in human aortic endothelial cells, ginsenoside-Rb₁ increased nitric oxide production [52]. Another study has shown that such stimulation by ginsenosides occurs in these cells via phosphorylation of glucocorticoid receptor, PI3K, eNOS, and Akt/protein kinase B [53]. Similarly, in a canine model, ginsenoside Rg₃ induced vasodilation, indicating its role in improvement of arterial rigidity [54,55].

7. Ginseng and ginsenosides improve blood pressure

It was well known that ginsenoside Rg₃ ameliorates vascular dysfunction [56,57]. In addition, Korean Red Ginseng admonished arterial stiffness in hypertensive conditions [58]. Also, previous studies have shown that ginseng ameliorated low blood pressure, restoring it to normal level through the production of vascular endothelial cell-derived nitric oxide [59]. Furthermore, ginseng decreased blood pressure [60]. Recent reports have shown that ginseng has pharmacological and medicinal effects beneficial for blood pressure regulation, as lower doses have stronger antihypertensive effects than higher doses [61], and for improving blood circulation through vascular dilation. Also, ginseng has an antihypertensive effect by mediating the inhibition of myogenic activity of blood vessels [62,63]. These results show that ginseng treatment can ameliorate vasomotor function.

8. Ginseng and ginsenosides improve cardiac function

Ginsenosides protect the heart against cardiotoxicity induced by doxorubicin and inhibit the cardiac hypertrophy induced by monocrystaline in a rat model [64,65]. Ginsenoside Rg₁ protected against left ventricular hypertrophy caused by aorta coarctation produced through nitric oxide production [64]. In addition, ginsenoside Rb₁ protected against myocardial infarction after ischemia and reperfusion [66]. Cardiac dysfunction caused by ischemia and reperfusion has been ameliorated through the glucocorticoid receptor- and estrogen receptor-activated pathways and the eNOS-dependent mechanism [67]. Also, ginsenoside Rg₁ decreased left ventricular hypertrophy, and *P. ginseng* inhibited apoptosis in cardiomyocytes by modulating Bcl-2 and caspase-3 during ischemia and reperfusion [68,69]. In addition, ginsenoside Rg₁ protected cardiomyocytes from oxidative injury through antioxidative effects and calcium modulation [70]. Also, total saponin, panaxadiol, and panaxatriol protect against ischemia and reperfusion injuries [71]. A previous study showed that ginsenoside Rb₁ inhibited cardiac dysfunction in diabetes induced by streptozotocin [72]. Another study has reported that ginseng inhibited cardiac hypertrophy and heart failure through Nhe-1 modulation and decrease of calcineurin activation [73]. Compound K has been shown to increase cardiac protection through nitric oxide production via the Akt/PI3K pathway [74]. These studies demonstrate that ginseng preserves cardiac function after myocardial tissue dysfunction.

9. Ginseng and ginsenosides inhibit platelet aggregation

There has been much research on ginseng for preventing platelet aggregation. Korean Red Ginseng shows an important effect on arterial thrombosis *in vivo*, which might be due to inhibition of

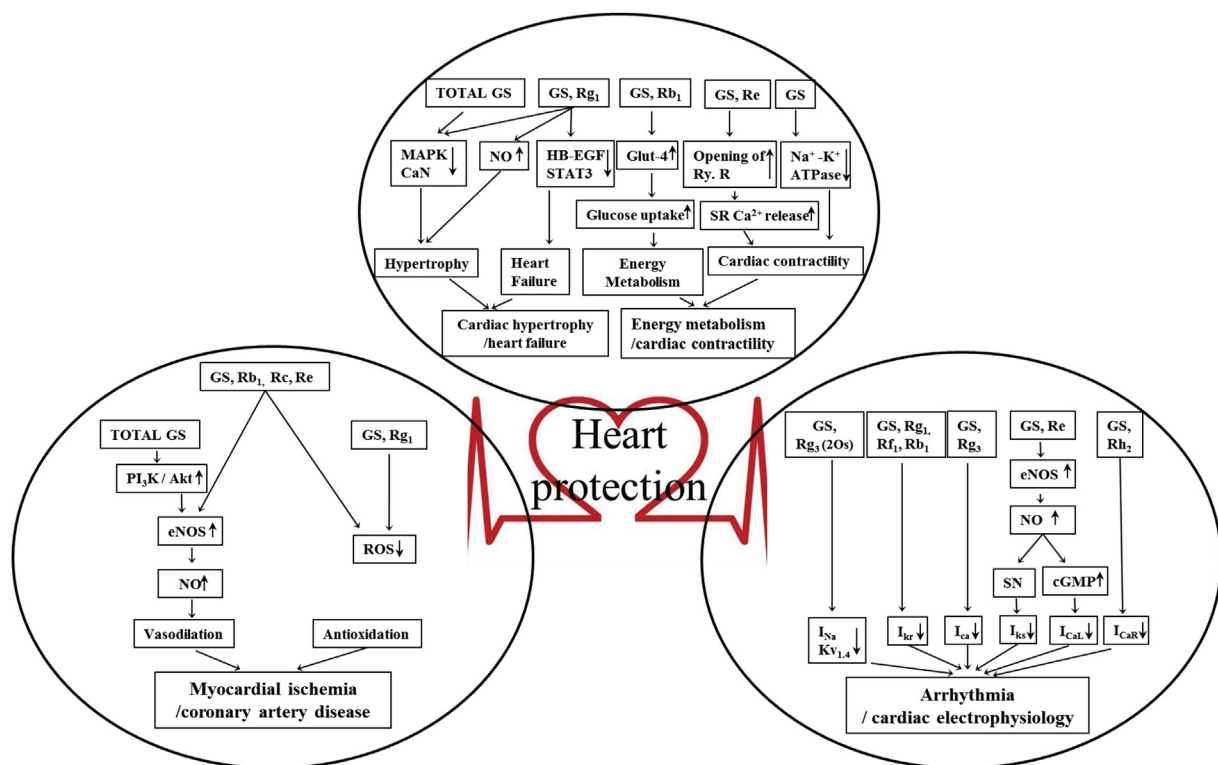


Fig. 2. Mechanisms of ginseng in protecting heart. eNOS, endothelial nitric oxide synthase; GLUT-4, glucose transporter-4; GS, ginsenoside; HB-EGF, heparin-binding EGF-like growth factor; I_{CaL}, L-type calcium channel current; I_{CaR}, R-type calcium channel current; I_{Kr}, rapidly activating component of delayed rectifier K⁺ current; I_{Ks}, slowly activating component of delayed rectifier K⁺ current; MAPK, mitogen-activated protein kinase; PI3K/Akt, phosphoinositide 3-kinase/protein kinase B; ROS, reactive oxygen species; RyRs, ryanodine receptors; SN, S-nitrosylation of channel protein; SR, sarcoplasmic reticulum; STAT3, signal transducer and activator of transcription 3.

Table 1
The effect of ginseng and ginsenosides on protecting heart [reference]

Ginseng and ginsenosides	Cardiac contractility	Arrhythmia	Cardiac infarction and coronary artery injury	Heart dysfunction
Ginseng	[89]	[26]	[86]	[90]
Ginsenosides Rg ₃		[91]		
Ginsenosides Rb ₁	[92]	[93]	[39]	[94]
Ginsenosides Re	[95]	[26]	[41]	
Ginsenosides Rf ₁		[93]		

platelet aggregation rather than anticoagulation, and this suggests that red ginseng treatment can be beneficial for individuals with cardiovascular impairment [75–77]. Another study reported that dihydroginsenoside Rg₃ powerfully inhibited platelet aggregation via downstream signaling such as cyclic adenosine-3', 5'-monophosphate (AMP) and extracellular signal-regulated kinase 2 [78]. *P. notoginseng* significantly decreased lipopolysaccharide-mediated microcirculatory troubles by preventing the adherence of leukocytes to the vascular wall, the degranulation of mast cell, and the release of various cytokines [79]. Also, ginsenosides Rg₆, Rk₃, Rh₄, Rs₃, Rs₄, Rs₅, and F4 extracted from processed ginseng were evaluated for platelet aggregation induced by adenosine diphosphate, collagen, and arachidonic acid. The results showed that ginsenosides Rs₃, Rs₄, and Rs₅ had weak effects on aggregation induced by the three stimulators. Coadministration of Korean Red Ginseng and warfarin showed some synergistic interactions in patients with cardiac valve replacement [80]. How does the dose of red ginseng affect the effect of warfarin? Warfarin must be administered with caution in patients with cardiac valve replacement. In ischemia and reperfusion injury of isolated rat hearts, coronary perfusion flow can be increased by total ginsenosides, indicating the protection of heart tissues by coronary artery dilation from I/R injury. This effective function of total ginsenosides is related to the activation of PI3K/Akt-eNOS pathway and NO formation [81]. Based on these results, studies suggest that *in vivo* ginseng or ginsenosides have an important antithrombotic effect that would be beneficial for individuals with thrombotic problems and cardiovascular diseases.

10. Ginseng and ginsenosides ameliorate lipid profile

Administration of red ginseng extract increased coronary flow in individuals with cardiac ischemia [82]. This suggests that blood circulation is improved via anticoagulant activity. It was previously reported that the hypoglycemic and hypolipidemic effects of red ginseng were dramatically improved by the *bifidus* fermentation procedure [83]. Although a hypercholesterolemic condition could increase the platelet aggregation activity, Korean Red Ginseng decreased platelet aggregation through the inhibition of diacylglycerol liberation in a high cholesterol diet [84]. In addition, saponin treatment inhibited atherosclerosis in ApoE-knockout mice through its anti-inflammatory effects and amelioration of the lipid profile [85,86]. Furthermore, ginsenoside Rd treatment inhibited atherosclerosis in ApoE-knockout mice [3]. These results suggest that treatment with ginseng or ginsenosides could ameliorate lipid profiles *in vivo*.

11. Ginseng and ginsenosides prevent myocardial ischemia

There are many reports that treatment with ginseng improved electrocardiogram, general symptoms, physical exercise capacity, and fluid metabolism in patients with coronary angina pectoris [87]. Many cardiac protective effects of ginseng depend on the antioxidant properties of the ginseng components in cardiomyocytes

[88–91]. Total ginsenosides, especially panaxatriol, provided powerful protection against myocardial ischemia and reperfusion [71]. Administration of total ginsenosides increased perfusion flow of the coronary artery dose-dependently, and this vasodilatory activity seemed to be mediated by activation of the phosphoinositide 3-kinase/protein kinase B-eNOS pathway, followed by improved NO production [92,93]. Interestingly, the vasodilatory effect of total ginsenosides was abolished by treatment with an inhibitor of NO synthase. Ginsenoside Rb₁ treatment established the vasodilating mechanism of porcine coronary arteries, which depends on upregulation of NO synthase and downregulation of superoxidases [94]. Ginsenoside Rb₁ as well as ginsenosides Rc and Re prevented vascular injury in porcine coronary arteries induced by the human immunodeficiency virus protease inhibitor, contributing to vasodilation by regulation of NO and superoxidase levels [95]. Also, ginsenoside Re protected cardiomyocytes from damage induced by various oxidants through a mechanism reliant on the scavenging of H₂O₂ and hydroxyl radicals. Another study reported that ginsenoside Rg₁ showed antioxidative effects and an effect on intracellular calcium homeostasis, protecting cardiomyocytes during hypoxia and reoxygenation periods. As described above, *Panax ginseng* and ginsenosides have multiple functions on cardioprotection and confirmation of the mechanisms is progressing (Fig. 2; Table 1).

12. Summary

The present review summarizes information regarding the efficacy of ginseng and ginsenosides on primary cardiovascular risk factors such as dysfunction of ion regulation, signal transduction problems, oxidative stress, platelet aggregation, hypertension, hyperlipidemia, and cardiac ischemia. Ginseng and ginsenosides play a primary role in preventing cardiovascular disease. As shown previously, ginseng and ginsenosides showed significant effects on cardiovascular disease through the inhibition of ROS formation, stimulation of NO generation, enhancement of vasomotor tone, improvement in blood circulation, and amelioration of lipid profile. However, the exact action mechanism of ginseng and ginsenosides remain unidentified. In the future, the specific mechanism of ginseng and ginsenoside against cardiovascular impairment must be studied. The common use of ginseng and ginsenosides as natural medicine requires verification to verify its efficacy and safety.

Conflicts of interest

The authors declare no competing financial interests.

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