Review article

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

Jong-Hoon Kim*
Department of Physiology, College of Veterinary Medicine, Chonbuk National University, Iksan, Republic of Korea

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A B S T R A C T

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, vasorelaxation, antiallergic, antidiabetic, and anticancer. To date, approximately 40 ginsenoside compounds 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 (Rg2, Rh1, Rh2, etc.) [13]. By chemical structure, 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) [14,15]. To date, over 30 ginsenosides have been reported and classified into the two categories: (1) the 20(S)-PD (ginsenosides Rb1, Rb2, Rd3, Rg3, Rh2, Rc, Rd, and Rf) and (2) the 20(S)-PT (ginsenosides Rg1, Rg3, 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, Rb1, Rb2, Rg1, Rg2, Rg3, Rh1, Rc, Rd, and Rf, 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 Rd 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 IkBz kinase [34]. Also, ginsenoside Rb2 and compound K inhibited the phosphorylation and degradation of IkBz [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 the inhibition of NFκB 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 F1α and decreases of lipid peroxidation [39]. In addition, ginseng prevented ROS production through the stimulation of nitric oxide. Ginsenoside-Rh1 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 monocrotaline 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 Rg3 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...
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 (cAMP) 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 cells, and the release of various cytokines [79]. Also, ginsenosides Rg6, Rk3, Rh4, Rs3, Rs4, and Rs5 had weak effects on aggregation induced by collagen, and arachidonic acid. The results showed that ginsenosides Rs3, Rs4, and Rs5 had weak effects on aggregation induced by the three stimulators. Co-administration 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 superoxide levels [94]. Ginsenoside Rb1 as well as ginsenosides Rc and Re prevented vascular injury in porcine coronary arteries induced by damage induced by various oxidants through a mechanism reliant on the scavenging of H2O2 and hydroxyl radicals. Another study reported that ginsenoside Rg1 showed antioxidant 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.

References

[1] Mahady GB, Gyllenhall C, Fong IH, Farnsworth NR. Ginseng: a review of safety and efficacy. Nutr Clin Care 2000;3:90–101.
[2] World Health Organization. WHO monographs on selected medicinal plants. Geneva: World Health Organization; 1999.
[3] Gillis CN. Panax ginseng pharmacology: a nitric oxide link? Biochem Pharmacol 1997;54:1–8.
[4] Buettner C, Yeh GY, Phillips RS, Mittleman MA, Kapchuk TJ. Systematic review of the effects of ginseng on cardiovascular risk factors. Ann Pharmacother 2006;40:83–95.
[5] Lim KH, Lim DJ, Kim JH. Ginsenoside-Re ameliorates ischemia and reperfusion injury in the heart: a hemodynamics approach. J Ginseng Res 2013;37:283–92.
[6] Artele AS, Wu JA, Yuan CS. Ginseng pharmacology: multiple constituents and multiple actions. Biochem Pharmacol 1999;58:1685–93.
[7] Zhou W, Chai H, Lin PH, Lumsden AB, Yao Q, Chen CJ. Molecular mechanisms and clinical applications of ginseng root for cardiovascular disease. Med Sci Monit 2004;10:187–92.
[8] Cheng Y, Shen LH, Zhang JT. Anti-amnestic and anti-aging effects of ginsenoside Rg1 and Rb1 and its mechanism of action. Acta Pharmacol Sin 2005;26:143–9.
[9] Lim KH, Ko D, Kim JH. Cardioprotective potential of Korean Red Ginseng extract on isoproteol-induced cardiac injury in rats. J Ginseng Res 2013;37:273–82.
Jin ZQ, Liu CM. Effect of ginsenoside Re on the electrophysiological activity of
Bai CX, Takahashi K, Masumiya H, Sawanobori T, Furukawa T. Nitric oxide-
Bai CX, Sunami A, Namiki T, Sawanobori T, Furukawa T. Electrophysiological
effect of ginseng and ginsenoside Re in Guinea pig ventricular myocytes. Eur J Pharmacol 2007:1381–
Sengupta S, Toh SA, Sellers LA, Skepper JN, Koolwijk P, Leung HW, Yeung HW, Wong RNS, Sasisekharan R, Fan TPD. Modulating angiogenesis: the yin and the yang in ginseng. Circulation 2004;110:1219–25.
Nah SY, Kim DH. Ginsenosides: are any of them candidates for drugs acting on the central nervous system? CNS Drug Rev 2007:13:381–
Lee KS, Chan K, Bensoussan A, Munroe MJ. Application of atmospheric pressure chemical ionisation mass spectrometry in the identification and determination of Panax species. Phytochem Anal 2007;18:146–50.
Kaneko H, Nakanishi K. Proof of the mysterious efficacy of ginseng: basic effects of medical ginseng, Korean red ginseng: its anti-stress action for prevention of disease. J PharmacoSci 2004:95:158–62.
Kasai R, Besso H, Tanaka O, Sairuwatari Y, Fuwa T. Saponins of red ginseng. Chem Pharm Bull (Tokyo) 1983;31:2120–5.
Kim SI, Park JH, Ryu JH, Park JD, Lee MH, Park JH, Kim TH, Baek NL. Ginsenoside Rg5, a genuine dammarane glycoside from Korean red ginseng. Arch Pharm Res 1996;19:551–3.
Park JD, Lee YH, Park JH, Jung JH, Sohn DH. A dammarane glycoside from Korean red ginseng. Phytochemistry 1997;44:931–3.
Park JD, Lee YH, Kim SI. Ginsenoside Rf2, a new dammarane ginsenoside from red ginseng (Panax ginseng). Arch Pharm Res 1998;21:615–7.
Kwon SW, Han SH, Kim JH, Pan YS, Park JH. Liquid chromatographic determination of less polar ginsenosides in processed ginseng. J Chromatogr A 2001;921:335–9.
Kim WY, Kim JM, Han SB, Lee SK, Kim ND, Park MK, Kim CK, Park JH. Steaming of ginseng at high temperature enhances biological activity. J Nat Prod 2000;63:1702–4.
Lee CH, Kim JH. A review on the medicinal potentials of ginseng and ginsenosides on cardiovascular diseases. J Ginseng Res 2014;38:161–71.
Jin ZQ, Liu CM, Sunami A, Namiki T, Sawanobori T, Furukawa T. Electrophysiological effects of ginseng and ginsenoside Re in Guinea pig ventricular myocytes. Eur J Pharmacol 2003;476:35–44.
Bai CX, Takahashi K, Masumiya H, Sawanobori T, Furukawa T. Nitric oxide-dependent modulation of the delayed rectifier K+ current and the L-type Ca2+ current by ginsenoside Re, an ingredient of Panax ginseng, in Guinea pig cardiomycocytes. Br J Pharmacol 2004;142:567–75.
Lee JH, Jeong SM, Kim JH, Lee BH, Yoon IS, Choi SH, Lee SM, Park YS, Lee JH, Kim SS, et al. Effects of ginsenosides and their metabolites on voltage gated Ca2+ channels. Mol Cells 2006:21:52–62.
Choi SH, Lee JH, Pyo MK, Lee BH, Shin TJ, Hwang SH, Kim BR, Lee SM, Oh JW, Kim HC, et al. Mutations Leu427, Asn428, and Leu431 residues within transmembrane helicase domains of human ATP-ase inhibited ginsenoside mediated L-type Ca2+ channel current inhibitions. Biol Pharm Bull 2009;32:1224–30.
Furukawa T, Bai CX, Kailara A, Ozaki E, Kawano T, Nakaya Y, Aways M, Sato M, Umezawa Y, Kurokawa J, Ginsenoside Re, a main phytosterol of Panax ginseng, activates cardiac sarcoplasmic reticulum channels via a nongenomic pathway of sex horm.
Furukawa T, Bai CX, Kailara A, Ozaki E, Kawano T, Nakaya Y, Aways M, Sato M, Umezawa Y, Kurokawa J, Ginsenoside Re, a main phytosterol of Panax ginseng, activates cardiac sarcoplasmic reticulum channels via a nongenomic pathway of sex horm. Mol Pharm 2006;70:1916–24.
Lee JH, Jeong SM, Lee BH, Noh HS, Kim BR, Kim JH, Rhim H, Kim HC, Kim KM, Nah SY. Prevention of ginsenoside-induced desensitization of Ca2+-activated Cl-current by microinjection of inositol hexakisphosphate in Xenopus laevis oocytes: involvement of GRK2 and beta-arrestin 1. J Biol Chem 2004;279:9912–21.
Xue JF, Liu ZJ, Hu JF, Chen H, Zhang JT, Chen NH. Ginsenoside Rb1 promotes neurotransmitter release by modulating phosphorylation of synapsins through a cAMP-dependent protein kinase pathway. Brain Res 2006;1106:91–8.
Choi K, Xu CX, Zhou YC, Chen Y, Zhu YG, Fang F, Chen LM. Ginsenoside Rg1 reduces MPTP induced substantia nigra neuron loss by suppressing oxidative stress. Acta Pharmacol Sin 2005;26:36–42.
Choi K, Kim M, Ryu J, Choi C. Ginsenosides compound K and Rh2 inhibit tumor necrosis factor-alpha-induced activation of the NF-kappaB and JNK pathways in human astrogial cells. Neurosci Lett 2007;421:37–41.
Bolli R. Superoxide dismutase 10 years later: a drug in search of a use. J Am Coll Cardiol 1991;17:231–3.
Li J, Ichikawa T, Jin Y, Hofseth LJ, Nagarkatti P, Nagarkatti M, Windust A, Cui T. An essential role of Nrf2 in American ginseng-mediated anti-oxidative actions in cardiomycocytes. J Ethnopharmacol 2010;130:222–30.
Sohn SH, Kim SY, Kim KD, Shin YS, Yang SO, Kim SY, Lee SW. A comparison of antioxidant activity of Korean White and Red Ginsengs on H2O2-induced oxidative stress in HepG2 hepatoma cells. J Ginseng Res 2009;33:424–50.
Chen X. Cardiovascular protection by ginsenosides and their nitric oxide releasing action. Clin Exp Pharmacol Physiol 1996;23:728–32.
produced by abdominal aorta coarctation in rats. Biol Pharm Bull 2010;33:631–5.

[65] Wu Y, Xia ZY, Dou J, Zhang L, Xu JJ, Zhao B, Lei S, Liu HM. Protective effect of ginsenoside Rb1 against myocardial ischemia/reperfusion injury in streptozocin-induced diabetic rats. Mol Biol Rep 2011;38:4327–35.

[66] Zhou H, Hou SZ, Luo P, Zeng B, Wang JR, Wang YF, Jiang ZH, Liu L. Ginseng protects rodent hearts from acute myocardial ischemia-reperfusion injury through ERK2 and cAMP-activated risk pathway in an endothelial NOS-dependent mechanism. J Ethnopharmacol 2011;135:287–98.

[67] Wang YL, Wang CY, Zhang BJ, Zhang ZZ. Shenfu injection suppresses apoptosis by regulation of Bcl-2 and caspase-3 during hypoxia/reoxygenation in neonatal rat cardiomyocytes in vitro. Mol Biol Rep 2009;36:365–70.

[68] Zhu D, Wu L, Li CR, Wang XW, Ma YJ, Zhong ZY, Zhao HB, Cui J, Sun SF, Huang XL, et al. Ginsenoside Rg1 protects rat cardiomyocyte from hypoxia/reoxygenation oxidative injury via antioxidant and intracellular calcium homeostasis. J Cell Biochem 2009;108:117–24.

[69] Kim TH, Lee SM. The effects of ginseng total saponin, panaxadiol and panaxatriol on ischemia/reperfusion injury in isolated rat heart. Food Chem Toxicol 2010;48:1516–20.

[70] Guo J, Gan XT, Haist JV, Rajapurohitam V, Zeidan A, Fanuq NS, Karmazyn M. Panax notoginseng Improving effect of post-treatment with neutral lipid peroxidation. Free Radic Biol Med 2009;46:614–9.

[71] Kim JH, Kim SW, Lee YC, Kim DH. Biological effects of total saponins of Panax ginseng C.A. Meyer on cardiovascular function. J Ginseng Res 2013;37:176–86.

[72] Jin YR, Yu JY, Lee BJ, You SH, Chung JH, Noh JY, Im BH, Han XH, Kim TJ, Shin KS, et al. Anti-inflammatory and antiplatelet activities of Korean red ginseng extract. Basic Clin Pharmacol Toxicol 2007;100:170–5.

[73] Lee WM, Kim SD, Park MH, Cho JY, Park HJ, Seo GS, Rhee MH. Inhibitory mechanisms of dihydroginsenoside Rg3 in platelet aggregation: critical roles of ERK2 and AMPK. J Pharm Pharmacol 2008;60:1531–7.

[74] Yang JY, Sun K, Wang CS, Guo J, Xue X, Liu YJ, Zhang J, Fan JY, Luo FL, Han JY. Improving effect of post-treatment with Panax notoginseng saponins on lipopolysaccharide-induced microcirculatory disturbance in rat mesentery. Clin Hemorheol Microcirc 2008;40:119–31.

[75] Lee YH, Lee BK, Choi YJ, Yun JK, Chang BC, Gwak HS. Interaction between warfarin and Korean red ginseng in patients with cardiac valve replacement. Int J Cardiol 2010;145:275–6.

[76] Yi XQ, Li T, Wang JR, Wong VK, Luo P, Wong YJ, Jiang ZH, Liu L, Zhou H. Total ginsenosides increase coronary perfusion flow in isolated rat hearts through activation of PI3K/Akt-eNOS signaling. Phytomedicine 2010;17:1006–15.

[77] Ahn CM, Hong SJ, Choi SC, Park JH, Kim JS, Lim DS. Red ginseng extract improves coronary flow reserve and increases absolute numbers of various circulating angiogenic cells in patients with first ST-segment elevation acute myocardial infarction. Phytother Res 2011;25:239–49.

[78] Trinh HT, Han SJ, Kim SW, Lee YC, Kim DH. Bifidus fermentation increases hypolipidemic and hypoglycemic effects of red ginseng. J Microbiol Biotechnol 2007;17:1127–33.

[79] Hwang SY, Son DJ, Kim IW, Kim DM, Sohn SH, Lee J, Kim SK. Korean red ginseng attenuates hypercholesterolemia-enhanced platelet aggregation through suppression of diacylglycerol liberation in high-cholesterol-diet-fed rabbits. Phytother Res 2008;22:778–83.

[80] Zhang YG, Zhang HG, Zhang CY, Fan JS, Li XH, Liu YH, Li SH, Lian XM, Tang Z. Panax notoginseng saponins attenuate atherosclerosis in rats by regulating the blood lipid profile and an anti-inflammatory action. Clin Exp Pharmacol Physiol 2008;35:1238–44.

[81] Liu G, Wang B, Zhang J, Jiang H, Liu F. Total Panax notoginsenosides prevent atherosclerosis in apolipoprotein E-knockout mice: role of down-regulation of CD40 and MMP-9 expression. J Ethnopharmacol 2009;126:350–4.

[82] Li J, Xie ZZ, Tang YB, Zhou JG, Guan YY. Ginsenoside-Rd, a purified compound from Panax notoginseng saponins, prevents atherosclerosis in apoE knockout mice. Eur J Pharmacol 2011;652:104–10.

[83] Yuan J, Guo W, Yang B, Liu P, Wang Q, Yuan H. 116 cases of coronary angiography treated with powder composed of Radix Ginseng, Radix Notoginseng and Succinum. J Tradit Chin Med 1997;17:14–7.

[84] Maffei Facino R, Carini M, Aldini G, Berti F, Rossini G. Panax ginseng administration in the rat prevents myocardial ischemia-reperfusion damage induced by hyperbaric oxygen: evidence for an antioxidant intervention. Planta Med 1999;65:614–9.

[85] Zhang D, Yasuda T, Yu Y, Zheng P, Kawabata T, Ma Y, Okada S. Ginseng extract scavenges hydroxyl radical and protects unsaturated fatty acids from decomposition caused by iron-mediated lipid peroxidation. Free Radiol Med 1996;20:145–50.

[86] Chai H, Zhou W, Lin F, Lumsden A, Yao Q, Chen C. Ginsenosides block HIV protease inhibitor ritonavir-induced vascular dysfunction of porcine coronary arteries. Am J Physiol Heart Circ Physiol 2005;288:H2965–71.

[87] Toh HT. Improved isolated heart contractility and mitochondrial oxidation after chronic treatment with Panax ginseng in rats. Am J Chin Med 1994;22:725–84.

[88] You JS, Huang HF, Chang YL. Panax ginseng reduces adriamycin-induced heart failure in rats. Phytother Res 2005;19:1018–22.

[89] Choi SH, Shin TJ, Lee BH, Choe DH, Choe H, Pyo MK, Hwang SH, Kim BR, Lee SM, Lee JH, et al. Ginsenoside Rg3 activates human KCNQ1 K+-channel currents through interacting with the K318 and V319 residues: a role of KCNE1 subunit. Eur J Pharmacol 2010;637:138–47.

[90] Kong HL, Wang JP, Li ZQ, Zhao SM, Dong J, Zhang WW. Anti-hypoxic effect of Panax ginseng attenuates atherosclerosis in rats. J Ethnopharmacol 2008;116:1516–20.

[91] Kong HL, Wang JP, Li ZQ, Zhao SM, Dong J, Zhang WW. Anti-hypoxic effect of Panax ginseng attenuates atherosclerosis in rats. J Ethnopharmacol 2008;116:1516–20.

[92] Kong HL, Wang JP, Li ZQ, Zhao SM, Dong J, Zhang WW. Anti-hypoxic effect of Panax ginseng attenuates atherosclerosis in rats. J Ethnopharmacol 2008;116:1516–20.

[93] Kong HL, Wang JP, Li ZQ, Zhao SM, Dong J, Zhang WW. Anti-hypoxic effect of Panax ginseng attenuates atherosclerosis in rats. J Ethnopharmacol 2008;116:1516–20.