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Cardiovascular Diseases and *Panax ginseng*: A Review on Molecular Mechanisms and Medical Applications

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Ginseng is one of the most widely used herbal medicines and is reported to have a wide range of therapeutic and pharmacological applications. Ginseng may also be potentially valuable in treating cardiovascular diseases. Research concerning cardiovascular disease is focusing on purified individual ginsenoside constituents of ginseng to reveal specific mechanisms instead of using whole ginseng extracts. The most commonly studied ginsenosides are Rb_1, Rg_1, Rg_3, Rh_1, Re, and Rd. The molecular mechanisms and medical applications of ginsenosides in the treatment of cardiovascular disease have attracted much attention and been the subject of numerous publications. Here, we review the current literature on the myriad pharmacological functions and the potential benefits of ginseng in this area. *In vitro* investigations using cell cultures and *in vivo* animal models have indicated ginseng's potential cardiovascular benefits through diverse mechanisms that include antioxidation, modifying vasomotor function, reducing platelet adhesion, influencing ion channels, altering autonomic neurotransmitters release, and improving lipid profiles. Some 40 ginsenosides have been identified. Each may have different effects in pharmacology and mechanisms due to their different chemical structures. This review also summarizes results of relevant clinical trials regarding the cardiovascular effects of ginseng, particularly in the management of hypertension and improving cardiovascular function.

Keywords: *Panax ginseng*, Cardiovascular disease(CVD), Myocardial ischemia, Vasomotor tone, Lipid profile, Antioxidants

INTRODUCTION

Cardiovascular disease (CVD) is an important problem among the 400 million indigenous populations around the world, and have been included in the World Health Organization '2008-2013 Action plan for non-communicable diseases' [1]. CVD, which encompasses a spectrum of diseases including coronary artery disease, peripheral vascular disease, congestive heart failure, dyslipidemias, and hypertension, affects millions of Americans and is perennial among the leading causes of morbidity and mortality [2]. These diseases are common and occur in infants, children, and adults of both genders, affecting people of all races and ethnicities. The lifetime risk for a 40-year-old developing coronary heart disease is roughly 50% for men and 32% for women [3]. Over the past 50 years, it has become clear that the cascade of thrombotic events following atherosclerotic plaque rupture causes occlusion of the coronary artery, which interrupts the supply of blood and oxygen to the myocardium, resulting in infarction. Myocardial necrosis following infarction is followed by heart failure, myocardial rupture, or arrhythmia [4]. Despite enormous strides in the last five decades, myocardial infarction, stroke, and sudden death remain the principal causes of morbidity and mortality in industrialized nations. Among the most

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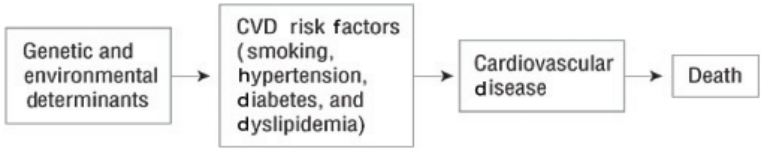

Fig. 1. Pathway relating cardiovascular disease (CVD) mortality. The established CVD risk factors lie in the middle of a chain of events that leads to cardiac death.

important of these CVD are dyslipidemia, hypertension, age, smoking status, insulin resistance, diabetes mellitus, and family history for premature coronary artery disease [5]. Also, atherosclerosis and acute coronary syndrome are now recognized as manifestations of vascular inflammation [6,7]. Risk factors for CVD promote endothelial dysfunction. Dysfunctional endothelial cells express adhesion molecules, which promote the binding and influx of inflammatory white blood cells (T-cells and mast cells) into the subendothelial space [8]. White blood cells produce interleukins, cytokines, and reactive oxygen species, which create an inflammatory focus within the arterial wall. Atherogenic lipoproteins such as low-density lipoprotein access the subendothelial space where they become trapped within the network of intercellular matrix proteins and undergo enzymatic oxidative modification, aggregation, and, ultimately, uptake by macrophages. This process leads to the development of foam cells [9,10].

Heart disease is the leading cause of death among all ages, and cardiac infarction remains the major cause of death (Fig. 1) [11,12]. This is the foremost reason why CVD is a major area of longevity research.

Ginseng has been used for over 2,000 years, in the belief that it is a panacea and promotes longevity. *Panax ginseng* is a traditional medicinal plant that has been used therapeutically for millennia in the Orient. Particularly in Korea, China, and Japan, it is the most valuable of all medicinal herbs. The name *Panax* means 'all healing,' which describes the traditional belief that ginseng has properties to heal all aspects of the body. The most common ginsengs are Korean red ginseng (*P. ginseng* Meyer), Chinese ginseng (*P. notoginseng*) and American ginseng (*P. quinquefolium* L.). Despite this rich history, the basis of the plant's medicinal prowess was unknown until the isolation of the active constituents (ginsenosides) beginning in 1963 [13,14]. Much effort has since been focused on evaluating the function and elucidating the molecular mechanism of each ginsenoside. This is reflected in the exploding number of PubMed cited publications on ginseng and ginsenosides since 1975. Research now focuses on the study of purified individual ginsenosides instead of using whole ginseng root [15-20]. Each ginsenoside may have different pharmacologic effect(s) and mechanism(s) reflective of their different structures. Approximately 40 ginsenosides have been identified as of 2012, and the various methods of separation and analysis are well-reviewed [21]. The most commonly studied ginsenosides are Rb_1, Rg_1, Rg_3, Re, and Rd. A detailed review about the anti-amnestic and anti-aging effects and action mechanisms of Rb_1 and Rg_1 has been published [20].

Moreover, ginseng and its ginsenoside constituents are thought to possess vasorelaxation, anti-oxidation, anti-inflammation, and anti-cancer activities. Ginsenosides also showed the effects on the central nervous system and the peripheral nervous system [22]. Furthermore, ginseng's long-lasting prowess has been demonstrated as well as its enhanced benefit in a disease state than a healthy state [23-25]. Additionally, a previous study reported the molecular mechanisms and cardiovascular clinical applications of ginseng [19].

Koreans have traditionally used *P. ginseng* roots and root extracts to revitalize the body and mind, increase physical strength, prevent aging, and increase vigor. A new pharmacological concept of the tonic effect of ginseng has arisen [26], resulting in interest and attention by explaining the basic pharmacology of ginseng with adaptogen effects. Ginseng use is common in individuals who have cardiovascular risk factors, such as hypertension, hypercholesterolemia, and oxidative damage. Yet, its' cardiovascular safety and efficacy are unclear. This review summarizes the current knowledge regarding the efficacy of ginseng on the major cardiovascular risk factors of blood pressure, cardiac ischemia, vasomotor activity, lipid profile, and oxidative stress.

EFFICACY OF REGULATING INTRACELLULAR ION CHANNELS

In the heart, calcium ion (Ca^{2+}) is crucial for the regulation of contraction and intracellular signaling, which are vital to heart function. Ca^{2+}-activated signaling pathways must function against a background of large, rapid, and tightly regulated changes in intracellular free Ca^{2+} concentrations during each contraction and relaxation

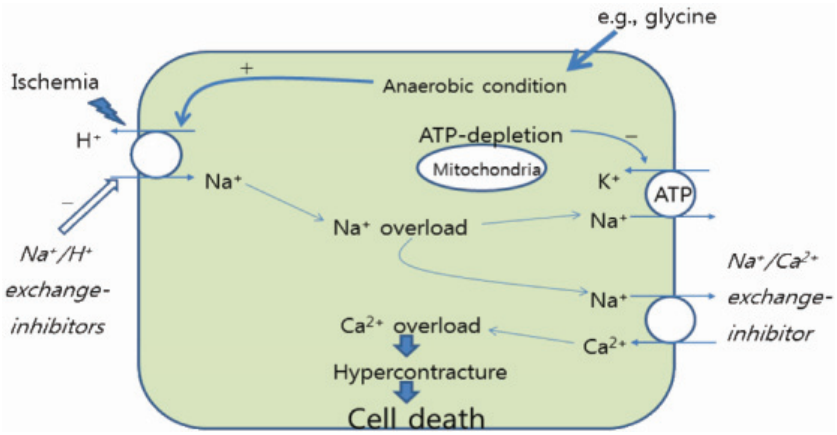

Fig. 2. Role of sodium- and calcium-overload in the pathogenesis of hypercontracture after cardiac ischemia/reperfusion.

cycle (Fig. 2).

Ginsenoside Rb_1 inhibits cardiac hypertrophy in a rat model [27]. Ginsenoside Rd reverses basilar hypertrophic remodeling in stroke-prone renovascular hypertensive rats as a new voltage-independent Ca^{2+} entry blocker [28]. Also, the effect of sugar position in ginsenosides on inhibitory potency of Na^+/K^+-ATPase activity has been described [29]. Another study reported that mutations in the Leu427, Asn428, and Leu431 residues attenuate ginsenoside-mediated L-type Ca^{2+} channel current inhibition [30]. The data indicate that ginsenosides inhibit Ca^{2+} entry, and so may ameliorate cardiac function.

EFFICACY OF ADJUSTING BLOOD PRESSURE

Ginseng use was once rumored to increase blood pressure to unhealthy levels. While ginseng can elevate blood pressure, this generally occurs with low blood pressure, which helps restore blood pressure to normal; ginseng also lowers high blood pressure [31]. Biochemical and pharmacological activities of ginseng related to blood pressure control are being clarified with continued research. The vasodilation action of *P. ginseng* improves blood circulation [32]. Korean red ginseng has an antihypertensive effect, which appears to be related to lower rather than higher doses of ginsenosides [33]. In addition, the blood pressure lowering activity of *P. ginseng* is due to promotion of vascular endothelial cell-derived nitric oxide (NO) secretion [32,34]. Furthermore, a mixed aqueous extract of salvia miltiorrhiza and *P. notoginseng* demonstrated anti-hypertensive effects by inhibition of arterial myogenic responses [35]. The collective observations indicate that ginseng normalizes blood pressure and improves blood circulation.

EFFICACY OF IMPROVING MYOCARDIAL PROTECTION

Ginseng has been used for treatment of heart failure and to protect tissues from damage when an organism is under stress [36]. These attributes come with the added advantage of an absence of harmful side effects. Saponins from *P. notoginseng* protect against doxorubicin-induced cardiotoxicity in mice [37]. Total ginsenosides inhibit right ventricular hypertrophy in rats [38] and nitric oxide functions in ginsenoside Rg_1-induced protection against left ventricular hypertrophy in rats [39]. Ginsenoside Re suppresses electromechanical alternans in cat and human cardiomyocytes [40] and ginsenoside Rb_1 preconditioning protects against myocardial infarction after regional ischemia and reperfusion [41]. Left ventricular hypertrophy in rats is also inhibited by ginsenoside Rg_1 [42]. Another study suggested that *P. ginseng* suppresses apoptosis by regulation of Bcl-2 and caspase-3 during hypoxia/reoxygenation in neonatal rat cardiomyocytes [43]. The effects of wild ginseng and astragali radix pharmacopuncture have been compared on the autonomic nervous system and heart rate variability [44]. In addition, ginsenoside Rg_1 protects rat cardiomyocyte from hypoxia/reoxygenation oxidative injury via antioxidant and intracellular calcium homeostasis [45]. The protective effects of ginseng total saponin, panaxadiol, and panaxatriol on ischemia/reperfusion injury have been documented in isolated rat heart [46]. The protective role of ginsenoside Rb_1 against myocardial ischemia/reperfusion injury in streptozotocin-induced diabetic rats has been reported [47], as has the role of ginseng in reducing adverse post-myocardial remodeling [48]. The results of another study supported the suggestion that ginseng inhibits cardiomyocyte hypertrophy and heart failure via

Nhe-1 inhibition and attenuation of calcineurin activation [49]. Furthermore, compound K, a metabolite of ginsenosides, bestows nitric oxide-mediated cardiac protection via the Akt/phosphoinositol-3-kinase (PI3K) pathway [50]. Ginseng also protects from cardiac injury by acute myocardial ischemia-reperfusion in rodents through Gr/Er-activated risk pathway in an endothelial nitric oxide synthase (eNOS)-dependent mechanism [51]. The collective data conclusively indicate that ginseng protects from myocardial damage.

EFFICACY OF REGULATING VASCULAR ENDOTHELIAL CELLS

Individuals with peripheral arterial disease typically have atherosclerotic disease affecting several vascular beds, including coronary, cerebral, and renal beds [52]. This may account for both the increased cardiac morbidity and mortality [53]. Scientifically proven pharmacological effects of ginseng on vascular endothelial cells are as follows. Ginsenoside Rb_1 has effects on human umbilical vein endothelial cells *in vitro* [54]. Water extract of Korean red ginseng exhibits angiogenesis by activating the PI3K/Akt-dependent extracellular signal-regulated kinase 1/2 and eNOS pathways in human umbilical vein endothelial cells [55]. Ginsenosides also exhibit angiomodulatory and neurological effects [56]. Moreover, ginsensoside Re activates potassium channels of vascular smooth muscle cells through PI3k/Akt and NO pathways [57]. In addition, ginsenoside-Re has non-genomic effects of in endothelial cells via the glucocorticoid receptor [58]. Ginsenoside Rb_1 may attenuate capillary morphogenesis by the action of oestrogen receptor beta agonist [59] and induces the signaling pathway of NO production in human aortic endothelial cells [60]. Ginsenoside Rg_1 and Re isolated from *P. ginseng* are stable angiogenic agents [61]. Extracts from *P. notoginseng* and *P. ginseng* fruit enhance vascular endothelial cell proliferation and migration *in vitro* [62]. Moreover, experiments using fluorescent transgenic mice established the angiogenic effect of ginsenoside Rg_1 from *P. ginseng* [63]. The role of this ginsenoside Rg_1 in the induction of angiogenesis was also established in another study [64]. The angiogenic effect of saponin extract from *P. notoginseng* on human umbilical vein endothelial cells *in vitro* and zebrafish *in vivo* has been described [65]. The results of another study suggested that *P. notoginseng* reduces atherosclerotic lesions in ApoE-deficient mice and inhibits tumor necrosis factor-alpha-induced endothelial adhesion molecule expression and monocyte adhesion [66]. Ginsenoside Rg_3 increases NO production via increases in phosphorylation and expression of eNOS [67]. Compound K inhibits basic fibroblast growth factor-induced angiogenesis through regulation of p38 mitogen-activated protein kinase and Akt in human umbilical vein endothelial cells [68]. Ginsenoside Rg_1 induces angiogenesis via non-genomic crosstalk of glucocorticoid receptor and fibroblast growth factor receptor 1 [69] and mediates the microenvironment-dependent endothelial differentiation of human mesenchymal stem cells *in vitro* [70]. Furthermore, ginsenoside Rb_1 protects against endothelial cell damage and stimulates ghrelin expression induced by hyperhomocysteine [71]. These collective observations suggest that ginseng saponin protects vascular endothelial cells via cellular signaling pathway.

EFFICACY OF REGULATING VASOMOTOR FUNCTIONS

The cardiovascular effects of ginseng and individual ginsenosides have been amply reviewed. Many reports describe transient vasodilator actions, in some cases followed by vasoconstriction and an increase in blood pressure. The endothelium contributes to the control of vascular smooth muscle tone by production and release of NO, which accounts for the biological activity of the endothelium-derived relaxing factor [72-74]. Ginsenosides have been shown to stimulate NO production in several systems. One study examined purified ginsenoside Rb_1-induced NO production in human aortic endothelial cells [60]. Another study reported that this ginsenoside increased the phosphorylation of glucocorticoid receptor, PI3K, Akt/protein kinase B, and eNOS, leading to increased NO production in human umbilical vein endothelial cells [75]. Other studies investigated the relaxation mechanism of ginsenoside Rg_3 using isolated canine corpus cavernosum [76] and demonstrated the effects of Korean red ginseng and its isolated ginsenosides and polysaccharides on arterial stiffness in healthy individuals [77]. Studies with ginsenoside Rg_3 reported induced vascular smooth muscle dysfunction and remodeling [78] and the inhibition of angiotensin II-induced vascular smooth muscle cell proliferation [79]. The effects of total saponins of *P. notoginseng* on aortic intimal hyperplasia and the expression of cell cycle protein and extracellular matrix in rats has been reported [80]. Finally, the benefit of Korean red ginseng on arterial stiffness in subjects with hypertension was reported [81]. Together, these results indicate that ginseng and ginsenosides ameliorate vasomotor function.

EFFICACY OF IMPROVING BLOOD CIRCULATION

Reports have documented ginseng's inhibitory effects on platelet aggregation [82] and endotoxin-induced disseminated intravascular coagulation [83], which has led to the use of ginseng, particularly Korean red ginseng, as an anti-thrombotic and fibrinolytic agent [84]. The role of ginsenoside Rg_3 in the inhibition of platelet aggregation has been described [85]. The role of ginsenosides in protecting human erythrocytes against hemin-induced hemolysis has been described [86]. Screening of anti-platelet aggregation agents from *P. notoginseng* can be done using human platelet extraction [87]. *P. notoginseng* saponins improve the post-treatment effects on lipopolysaccharide-induced microcirculatory disturbance in rat mesentery [88]. Anti-platelet and anti-coagulant effects of *P. notoginseng* were described in a comparison of raw and steamed *P. notoginseng* with *P. ginseng* and *P. quinquefolium* [89]. The platelet anti-aggregating activity of ginsenosides isolated from ginseng has been reported [90,91]. Another study documented the interaction between warfarin and Korean red ginseng in patients with cardiac valve replacement [92]. Total ginsenosides increase coronary perfusion flow in isolated rat hearts by activating PI3K/Akt-eNOS signaling [93]. Red ginseng extract improves coronary flow reserve and increases absolute numbers of various circulating angiogenic cells in patients with acute myocardial infarction [94]. Overall, these results suggest that ginseng may improve blood circulation by inhibiting platelet aggregation and coagulation activity.

EFFICACY OF ADJUSTING BLOOD LIPID PROFILE

Metabolic syndrome – defined as a cluster of three of insulin resistance and glucose intolerance, abdominal obesity, hypertension, low high density lipoprotein cholesterol, and hypertriglyceridemia – has become a global epidemic. The prevalence of metabolic syndrome in adults has been increasing rapidly in the past decades in most western countries, and the situation is even worse in people over 60-years-of-age [95]. Given the fact that people who have metabolic syndrome are susceptible to atherosclerotic CDV [96], effective and feasible therapeutic strategies are urgently needed for the treatment of complications of metabolic syndrome. In recent years, more attention has been paid to bioactive components from P. ginseng. Particularly, it was reported that *P. ginseng* saponin reduces weight gain in mice [97]. Bifidus fermentation was shown to increase the hypolipidemic and hypoglycemic effects of red ginseng [98]. Korean red ginseng attenuates hypercholesterolemia-enhanced platelet aggregation by suppressing diacylglycerol liberation in rabbits fed a diet high in cholesterol [99]. *P. notoginseng* saponins attenuate atherosclerosis by regulating the lipid profile and have an anti-inflammatory action in rats [100] and atherosclerosis is inhibited by total P. notoginsenosides in apolipoprotein E-knockout mice [101]. Also, cholesterol ester can be decreased by *P. notoginseng* saponins by the up-regulation of the ATP-binding cassette transporter A1 in foam cells [102]. The anti-hyperlipidemic effects of acidic polysaccharide from Korean red ginseng were reported [103]. *P. notoginseng* saponins attenuate atherogenesis in rabbits [104] and radix notoginseng has hypolipidemic and anti-oxidant activities in rats fed a high fat diet [105]. Ginsenoside-Rd prevents atherosclerosis in ApoE-knockout mice [106]. Overall, these results suggest that *P. ginseng* improves the lipid profile.

OXIDATION AND GINSENG

The production of reactive oxygen species (ROS) from various cellular metabolic processes caused by the restoration of coronary flow after cardiac ischemia is thought to contribute to myocardial damage [107-109]. ROS cause non-specific damage to lipids, proteins and DNA, leading to an alteration or loss of the cellular function. The abrupt rise in ROS as a result of the reoxygenation of ischemic or hypoxic cardiac muscle has been associated with a partially irreversible inhibition of mitochondrial respiration [110]. Alterations in generation and/or use of energy are thought to be important contributing factors to the observed dysfunction caused by ischemia reperfusion injury [111]. It is recognized that a free radical that is produced in excess of what is reasonably sufficient in the body may induce CVD. Therefore, extensive studies have been conducted on the cardioprotective effects of ginseng against free radical damage.

EFFICACY OF ANTI-OXIDANT ACTIVITY

The scientifically-proven pharmacological effects of ginseng against oxidative damage are as follows. Ginseng and ginsenosides have an anti-oxidant effect that is manifest as an inhibited increase in harmful free radical formation and lipid peroxidation [112-116]. Ginsenosides Rg_2 and Rh_1 protect from oxidation-induced impairment

of erythrocyte membrane properties [117]. *P. ginseng* polysaccharide is effective in the regulation of energy metabolism and protection of mitochondria [118]. Studies with American ginseng reported the mediation of anti-oxidant actions via Nrf2 in cardiomyocytes [119] and ginseng-related increased activity of the antioxidant enzymes, superoxide dismutase and glutathione peroxidase in rats [120]. Another *in vivo* study reported that ginsenosides protected against myocardial reperfusion damage with a concomitant increase in 6-keto-prostaglandin F1a and a decrease in lipid peroxidation, and also protected rabbit pulmonary and aortic endothelium against electrolysis-induced free radical damage [121]. Ginsenosides also protected rabbit pulmonary endothelium from injury induced by a variant of ROS [15]. Also, it was reported that ginseng prevented manifestations of ROS injury by promoting the release of NO. Endothelial dysfunction induced by homocysteine and human immunodeficiency virus protease inhibitors can be effectively blocked by Rb_1 and other ginsenosides [122,123], confirming the role of ginsenoside Rb_1 and other ginsenosides in blocking ROS production. In addition, ginsenoside Re possesses anti-oxidant effects in cardiomyocytes [124]. Ginsenosides exert their anti-oxidant ability by increasing internal antioxidant enzymes and acting as a free-radical scavenger [125-127]. Moreover, individual ginsenosides behave as an anti-oxidant if glucose is attached to the 20-position of the triterpene dammarane, such as Re, Rd, and R_1, but as a pro-oxidant if there are no sugar moieties attached to the 20-position of the ginsenoside such as Rg_3, Rh_2, and Rg_2 [128]. If a glucose is attached to the 6-position instead of 20-position sugar moieties, however, the ginsenoside still act as an anti-oxidant (e.g., Rh_1) [128]. Overall, these results suggest that ginseng may inhibit oxidative damage due to prevention of ROS generation.

CONCLUSION

Ginseng is a traditional herbal medicine whose history stretches back millennia. The basis of ginseng's prowess is its' many active constituent ginsenosides. Ginseng has extensive pharmacological activies and specific mechanisms of action. Ginsenosides can inhibit ROS production, stimulate NO production, increase blood circulation, ameliorate vasomotor tone, and adjust lipid profile. Additionally, many studies indicate that ginsenosides have a multitude of activities in both physiological and/or pathologic conditions concerning with CVD. How these effects relate to the ginsenoside structures are still not yet fully understood. Future cardiovascular studies involving each ginsenoside should include the mechanisms of action in more detail, with emphasis on specificity, structure and function relationship, detailed pharmacokinetics and toxicity researches, and therapeutic studies in both animal and human models.

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