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Review Article

Adaptogenic effects of *Panax ginseng* on modulation of cardiovascular functionsMuhammad Irfan¹, Yi-Seong Kwak², Chang-Kyun Han², Sun Hee Hyun^{2,**},
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ABSTRACT

Cardiovascular diseases are a rapidly growing epidemic with high morbidity and mortality. There is an urgent need to develop nutraceutical-based therapy with minimum side effects to reduce cardiovascular risk. *Panax ginseng* occupies a prominent status in herbal medicine for its various therapeutic effects against inflammation, allergy, diabetes, cardiovascular diseases, and even cancer, with positive, beneficial, and restorative effects. The active components found in most *P. ginseng* varieties are known to include ginsenosides, polysaccharides, peptides, alkaloids, polyacetylene, and phenolic compounds, which are considered to be the main pharmacologically active constituents in ginseng. *P. ginseng* is an adaptogen. That is, it supports living organisms to maintain optimal homeostasis by exerting effects that counteract physiological changes caused by physical, chemical, or biological stressors. *P. ginseng* possesses immunomodulatory (including both immunostimulatory and immunosuppressive), neuro-modulatory, and cardioprotective effects; suppresses anxiety; and balances vascular tone. *P. ginseng* has an antihypertensive effect that has been explained by its vasorelaxant action, and paradoxically, it is also known to increase blood pressure by vasoconstriction and help maintain cardiovascular health. Here, we discuss the potential adaptogenic effects of *P. ginseng* on the cardiovascular system and outline a future research perspective in this area.

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1. Introduction

Adaptogens are incredible natural substances that help the body to adapt stress, maintain or normalize metabolic functions, and restore systemic equilibrium. They enhance the resistance against acute or chronic stress and several other stressors (e.g., biological, physical, emotional and environmental). Adaptogens are usually unique from other constituents as they possess significant ability to restore the equilibrium, modulate nervous and immune system, and maintain the optimal homeostasis. Decades ago, Brekhman [1] coined the term adaptogen and defined that an adaptogen is nontoxic at therapeutic dose, produces nonspecific resistance to stress, and has the ability to normalize homeostasis [2–4].

Cardiovascular diseases (CVDs) are a leading cause of death worldwide. In 2005, the World Health Organization claimed that CVDs accounted for 30% of all deaths and included CVD in the World Health Organization 2008–2013 Action Plan for non-communicable diseases. In Europe, CVD causes 42% of deaths in men and 52% of deaths in women. Coronary heart disease caused almost one in seven deaths, and heart failure caused one in nine deaths in the United States in 2013 [5–8].

CVD includes a number of diseases and conditions, such as coronary artery disease, heart attack, myocardial infarction, hypertension, and atherosclerosis [9]. Various risk factors are involved in CVD, including diabetes, hypertension, smoking, obesity, dyslipidemia [i.e., elevated low-density lipoprotein (LDL) and decreased

Abbreviations: A β , Amyloid-beta; AD, Alzheimer's disease; Akt, Protein kinase B; APP, Amyloid precursor protein; cGMP, Cyclic guanosine 3',5'-monophosphate; CVD, Cardiovascular disease; eNOS, Endothelial nitric oxide synthase; NO, Nitric oxide; PI3K, Phosphatidylinositol-3 kinase.

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high-density lipoprotein (HDL) cholesterol], and pathophysiological hyperactivation of platelets, which may contribute to thrombotic complications, subsequently leading to atherosclerosis, thrombosis, stroke, and heart attack [10,11]. Platelets also express amyloid precursor protein (APP), account for 95% of the circulating APP, and are the primary source of amyloid-beta (A β), a key pathogenic factor in Alzheimer disease (AD), which affects 26 million people globally [12,13].

Several proven therapeutic regimes hamper different conditions of CVD. Some pharmacological drugs are commercially available, such as antihypertensive, antihypotensive, antiplatelet, antithrombotic, and anticholesterol agents, but their benefits are often outweighed by the serious side effects and complications. In particular, antiplatelet drugs, such as aspirin, cause prolonged bleeding time and gastric ulcers [10]. Clopidogrel treatment can cause aplastic anemia and thrombocytopenic purpura [14,15], and antihypertensive drugs frequently cause sexual dysfunction [16]. Such evidence highlights an urgent need to develop a safer and more efficacious approach, with no or minimum side effects, to manage such ailments. In this regard, ethnomedicinal applications could be one of the best strategies to hamper CVD and related complications [17].

Panax ginseng Meyer has been traditionally used since ancient times against several ailments because of its vast therapeutic range. Several pharmacological compounds (more than 40 ginsenosides, polysaccharides, peptides, alkaloids, polyacetylene, and phenolic compounds) with therapeutic effects against various diseases and cardiovascular ailments have been identified in *P. ginseng* [18–20]. Owing to its ability to maintain homeostasis in the host, by producing potential restorative and beneficial effects, *P. ginseng* is also known as an adaptogen [21–24]. Over five decades ago, in 1969, Brekhman (a pioneer in the experimental studies of *P. ginseng*) [1] was the first to describe *P. ginseng* as an adaptogen because of its nonspecific and tonic effects. As an adaptogen, ginseng enhances physical performance, promotes vitality, and resists against stress and aging [1,23,24] via immunomodulatory (including both immunostimulatory and immunosuppressive) and neuro-modulatory effects, as well as vasomodulatory effects (e.g., regulating vascular endothelial tone and blood pressure), which may account for its antihypertensive or antihypotensive action. *P. ginseng* has also been proven to exert cardioprotective effects [9,18,20]. Here, we discuss the potential adaptogenic effects of *P. ginseng* on the modulation of the cardiovascular system.

2. Blood pressure and vascular tone (antihypertensive and hypertensive effects)

P. ginseng has been found to restore and normalize blood pressure [18] and, paradoxically, exert both antihypertensive [25–29] and antihypotensive effects [30–33]. A few studies reported that the blood pressure effect of *P. ginseng* extract is biphasic, with an initial transient fall, followed by a prolonged elevation [34–36]. The antihypertensive effects of *P. ginseng* extract have been associated with lower rather than higher doses of ginsenosides [27,37]. Tables

1 and 2 summarized the comparative antihypertensive and antihypotensive effects of *P. ginseng*.

2.1. Vasodilatory and antihypertensive mechanism

P. ginseng's antihypertensive effects are due to the promotion of vascular endothelial cell–derived nitric oxide (NO) secretion via the conversion of L-arginine to L-citrulline by endothelial nitric oxide synthase (eNOS). Constitutively produced NO further triggers cyclic guanosine 3',5'-monophosphate (cGMP) production, a cellular mediator of vascular smooth muscle relaxation, causing vasodilation and lowering of blood pressure, thereby normalizing vascular flow in hypertensive individuals [18,38–40]. Most of the ginsenosides (e.g., Rb1, Rc, Re, and Rg1) can activate and stimulate NO production, and Rg3 stimulates NO production through various mechanisms [18,21]. In general, NO production is stimulated via eNOS, which is regulated by activation of androgen receptor and phosphatidylinositol-4,5-bisphosphate 3-kinase/protein kinase B (PI3K/Akt) and mitogen-activated protein kinase/extracellular signal-regulated kinase pathways (Fig. 1). Most of the ginsenosides follow the aforementioned pathway. Rg3 mediates eNOS activation through glucocorticoid receptor and estrogen receptor signaling cascades via PI3K and c-Jun N-terminal kinase [21,41]. Another study showed that estrogen receptor- α (ER- α) directly interacts with PI3K and modulates its activity in human vascular endothelial cells [42]. Hien et al [41] revealed that Rg3 has weak agonistic activities on both ER and glucocorticoid receptor (GR), but ER activation is critical for PI3K/Akt-mediated eNOS phosphorylation by Rg3. Rg1 also shows estrogenic activity via ER- α [43].

2.2. Vasoconstrictive and antihypotensive mechanism

A few decades back, Siegel [44] proposed that low doses of *P. ginseng* increase blood pressure. Recently, Chen et al [33] further concluded that ginseng stabilizes low blood pressure and improves compensatory response to acute volume change during hemodialysis in patients with intradialytic hypotension via activation of vasoconstrictors *i.e.*, endothelin-1 and angiotensin-II, which target vascular smooth muscle (VSM) to induce contraction. In another study, it was stated that a possible mechanism of vasoconstriction by the total ginseng saponins might involve the stimulation of adrenergic α_1 -receptors and membrane depolarization in the aorta, which seems to be associated with calcium influx [32]. There is no single ginsenoside reported to produce hypertensive effects but rather the total ginseng saponins. However, reports suggest that *P. ginseng* normalizes vascular tone and adjusts blood pressure, indicating its adaptogenic behavior.

3. Aphrodisiac properties (adaptogenic effects on physical and sexual performance)

P. ginseng is a vital constituent in traditional Chinese herbal medicine for the treatment of impotence and to increase sexual performance, and this could be correlated with its restorative, tonic,

Table 1
The antihypertensive effects of *P. ginseng*

Sample	Study type	Results	References
KRG	<i>In vitro, in vivo</i>	Vasoprotective effects through augmentation of NO signaling by inhibiting arginase	[25]
Total saponin of KRG	<i>In vivo</i>	Decreased blood pressure and induced reflex tachycardia, inhibition of the right ventricular hypertrophy	[26,29,37]
KRG	Human	Blood pressure–reducing effect	[27]
KRG	Human	Improvement of arterial hardening of hypertension by improving vascular motor function	[28]

KRG, Korean Red Ginseng.

Table 2
The antihypertensive effects of *P. ginseng*

Sample	Study type	Results	References
Ginseng extract	<i>In vivo</i>	Blood pressure increased	[30]
Ginseng	Human	Blood pressure increased	[31]
Total ginseng saponin	<i>In vivo</i>	Enhanced the contractile responses of vascular smooth muscle evoked by phenylephrine and/or KCl through increased extracellular Ca ²⁺ entry into the muscle cells	[32]
KRG		Elevate the nadir blood pressure and reduce the frequency of symptomatic intradialytic hypotension by increasing the nadir blood pressure	[33]

KRG, Korean Red Ginseng.

and adaptogenic properties. Studies reported that *P. ginseng* and ginsenosides (e.g., Rg1 and Rg3) improved erection and sexual performance by increasing serum testosterone, NO release, and cGMP accumulation by acting on the NO/cGMP pathway stimulation in the corpus cavernosum [23,24,45–48].

4. Balance vasomotor function and cardiac protection

Several studies have mentioned that *P. ginseng* and ginsenosides possess cardioprotective properties and also improve vasomotor function. Kim [18] summarized the cardioprotective effects of *P. ginseng* and ginsenosides, describing their potential to be effective in improving cardiac contractility (i.e., *P. ginseng*, Rb1, Re) [49–51], ameliorating arrhythmia (i.e., *P. ginseng*, Rb1, Re, Rg3, and Rf1) [52–54], and improving vasomotor function, which led to balanced vascular tone and normalized blood pressure. The observed

ginseng-mediated effects are due to enhanced contraction induced by stimulation of the adrenergic α_1 -receptors and membrane polarization via calcium influx [32]. *P. ginseng* causes vascular contractions and, paradoxically, stimulates vasorelaxation via modulation of vasomotor function, indicating its adaptogenic potential on the vascular endothelium.

5. Antiplatelet effects

Recently, we summarized and reported the antiplatelet and antithrombotic effects of *P. ginseng* and several ginsenosides [19,55–57]. There are many similarities and differences among the pharmacological and therapeutic effects of *P. ginseng*, and its ginsenosides, on vascular endothelial cells [18,20,21] and platelets [19], which may indicate its potential adaptogenic properties (Table 3). An interesting and classical example is that *P. ginseng* or

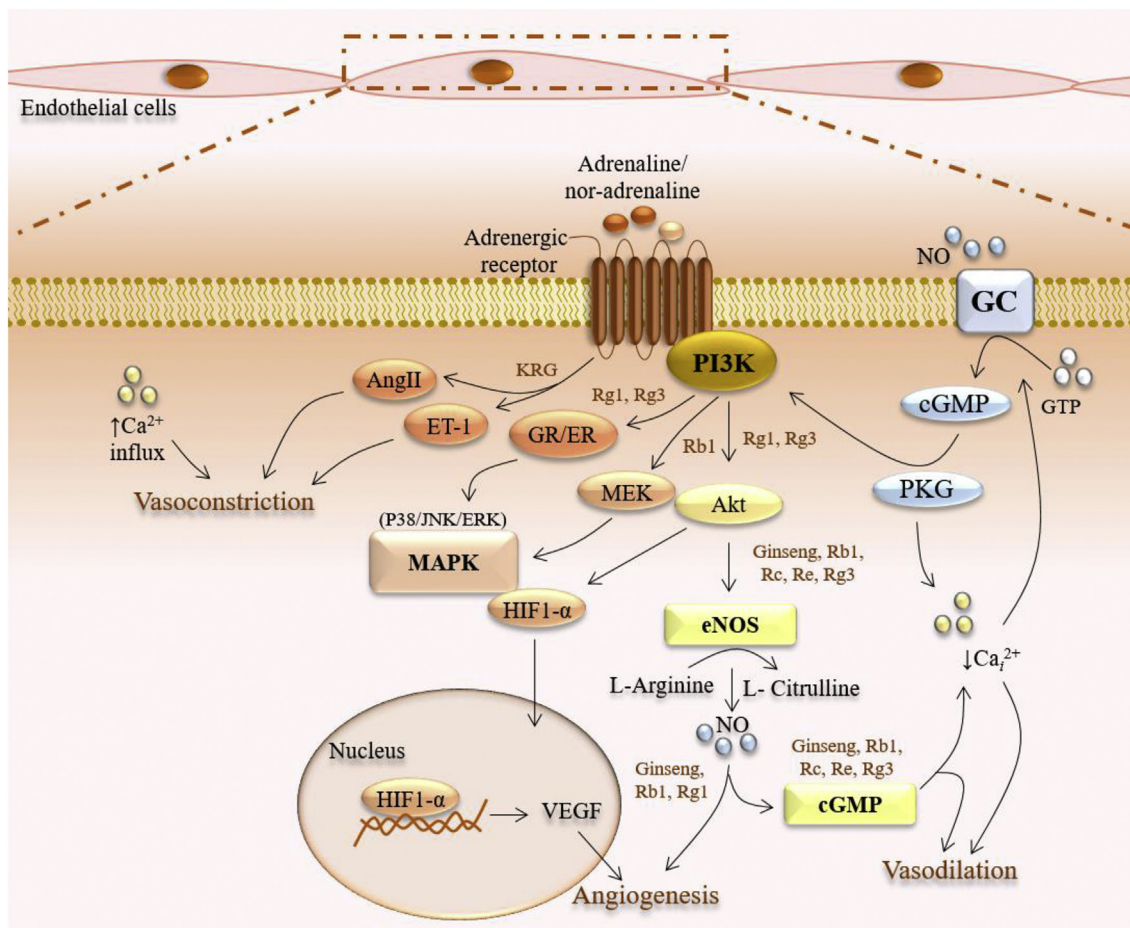


Fig. 1. Effect of *P. ginseng* and ginsenosides on vascular endothelial cells.

ginsenosides cause vasorelaxation by NO production through stimulation of the eNOS-PI3K/Akt pathway in vascular endothelial cells [18] but produce antiplatelet and antithrombotic effects by inhibiting the PI3K/Akt pathway [19]. Similarly, *P. ginseng* mainly potentiates cGMP in endothelial cells, whereas in platelets, it mainly enhances cyclic adenosine monophosphate secretion. It is noteworthy that *P. ginseng* and its various constituents play different functions in different cell types simultaneously to produce pharmacological and therapeutic effects in the body, indicating its potential adaptogenic behavior.

6. Blood viscosity and hemostasis

Thrombotic disorders or related cardiovascular ailments cause vascular stenosis (e.g., atherosclerosis or hypercholesterolemia), which contribute to increased blood viscosity and hypertension. Antiplatelet drugs are known to reduce blood viscosity and endothelial shear stress, thereby improving blood flow in arterial disease conditions [58,59]. Inactivation of platelets by such drugs may also lead to serious side effects that might outweigh their benefits. For example, aspirin causes increased bleeding time, and clopidogrel can induce thrombocytopenia [14,15]. As a nutraceutical, *P. ginseng* could help to minimize such drug-related side effects while providing multiple pharmacological and therapeutic benefits. Previously, we reported that *P. ginseng* and ginsenosides inhibit platelet activation, with no or minimal effect on hemostasis compared with aspirin [57,60], accompanied by vasorelaxation and improved vascular function. Moreover, the lipid profile was improved due to increased HDL cholesterol and decreased LDL cholesterol [61–63], contributing to improving blood viscosity and flow. These data demonstrate the adaptogenic behavior of *P. ginseng* and suggest that it could be an alternative antiplatelet and antithrombotic agent, with minimum complications, to treat and prevent platelet-related cardiovascular diseases. Future studies could further explore mechanistic aspects.

7. Antihyperlipidemic properties (antihyperlipidemic and antiobesity effect)

Red ginseng acidic polysaccharide (RGAP) from *P. ginseng* recovers the activity and level of lipoprotein lipase reduced in both endogenous and exogenous hyperlipidemic rat models [64]. triglycerides (TG) is mainly decreased by lipoprotein lipase, which is a well-known enzyme that breaks down TG [65]. High-fat diet (HFD) induced obesity, which is associated with metabolic diseases [66]. One of them is atherosclerosis, commonly referred to as a hardening or furring of the arteries. Atherosclerosis is induced by the formation of multiple plaques characterized by abnormal lipid metabolism within the arteries [67]. RGAP-induced improvement in lipid profiles affected by the HFD including TG, HDL cholesterol, and LDL cholesterol suggests that it may enhance lipid metabolism

and prevent obesity. HFD-fed mice increase body weight and plasma leptin concentration [68], but RGAP inhibits the rise of leptin [69]. In addition, adiponectin is an adipose tissue-specific protein that circulates in human plasma at a high level. Rise of adipose has been accompanied by reduction in plasma glucose and increase in insulin sensitivity. Adiponectin increases insulin sensitivity by increasing tissue fat oxidation, resulting in reduced circulating fatty acid levels and reduced intracellular TG in the liver and muscle [70]. RGAP restores the abnormal or impaired levels of the important indicators, leptin and adiponectin, thus improving delaying of HFD-induced metabolic abnormalities [69]. These results demonstrate that RGAP regulates imbalances of leptin and adiponectin, which results in a metabolic disorder induced by HFD. Therefore, it indicates that RGAP can effectively improve anti-hyperlipidemia and HFD-induced impairments in obesity [64,69].

8. Alzheimer disease

As mentioned in the introduction (section 1), AD is a neurodegenerative disorder affecting more than 26 million people worldwide. It is characterized by tau pathology and deposition of A β in brain parenchyma in the form of plaques, accompanied by inflammation and neuronal damage. Platelets express APP, which contributes to more than 90% of the circulating APP, are the main source of A β deposition in cerebral blood vessels, and contribute to cerebral amyloid angiopathy in AD [12,71]. Literature shows that A β peptides stimulate platelet activation and enhance platelet aggregation and platelet thrombi in the vasculature, which further aggravate AD pathology after shrinkage or rupture of the blood vessel [72–75].

P. ginseng and ginsenosides are well known to inhibit platelet activation [19,60], and they have also been documented to ameliorate AD symptoms and improve cognitive functions [76–78]. There is a great possibility that *P. ginseng* and ginsenosides may ameliorate cognitive dysfunction and reduce A β deposition in patients with AD by inhibiting platelet activation. Conversely, ginseng and ginsenosides will evoke endothelium-dependent vasorelaxation, thereby reducing the chances of plaque rupture and vascular shrinkage. These data suggest that *P. ginseng* has a great ability to adapt and improve cardiovascular functions. On the basis of the current research, we strongly hypothesize that *P. ginseng* or ginsenosides could be a useful therapeutic candidate to ameliorate platelet-related AD pathology and improve vascular functions.

9. Structure–activity relationship

Among ginsenosides from the protopanaxatriols (PPTs) (e.g., Rg1 and Re) and protopanaxadiols (PPDs) (e.g., Rb1, Rc and Rg3), only the PPT group enhanced NO from endothelial cells, suggesting that individual ginsenosides may differ in their activity [38,79]. Nag et al have reported that differential effects of ginsenosides in

Table 3
Comparative effects of *P. ginseng* and ginsenosides on platelet and endothelial cells

Ginseng/ginsenoside	Platelets	Endothelial cells	Ginseng/ginsenoside
Rg3, 2HRg3, Rp1, Rp3, Ro, TS, NSF	↑ cAMP	↑ cGMP	Rb1, Rc, Re
Rg1, Rg2, Rg3, 2HRg3, Rp1, Rp3, Rp4, gintonin	Inhibit PI3K/Akt	Activate PI3K/Akt	Rb1, Rc, Re
Rg3, 2HRg3, Ro, Rp1, Rp3, Rp4, TS, NSF, gintonin	Inhibit MAPK	Activate MAPK	Rb1, Rc, Re
–	↑ NO in stimulated platelets	↑ NO via eNOS	Ginseng, Rb1, Rc, Re, Rg3
Rg3, 2HRg3, Rp1, Rp3, Ro, TS, NSF	↑ VASP phosphorylation	↑ Vasorelaxation	Ginseng, Rb1, Rc, Re, Rg3
Rb1, Rc, Re	↑ Antihypertension	↑ Antihypertension	Ginseng, Rb1, Rc, Re, Rg3
Ginseng, Rg3	Improved blood flow	Improved blood flow	Ginseng, Rb1, Rc, Re, Rg3, Rf1

NO, nitric oxide; MAPK, mitogen-activated protein kinase; PI3K/Akt, phosphatidylinositol-4,5-bisphosphate 3-kinase/protein kinase B; eNOS, endothelial nitric oxide synthase; TS, total saponin; NSF, non-saponin fraction; VASP, vasodilator-stimulated phosphoprotein.

anticancer activity and discussed structure–activity relationship among PPD- and PPT-type ginsenosides [80]. Similarly, ginsenosides differ in their antiplatelet effects [19,56,57,60,81]. Ginsenosides contain different numbers and sites of sugar moieties/hydroxyl groups and possess different lipid solubilities and polysaccharides [82]. The number of sugar moieties, the number and position of hydroxyl groups, and stereoselectivity play a critical role in the pharmacological activity of the ginsenosides [80,81]. We have proposed earlier that structure–activity relationship is an important aspect in improving the efficacy of ginsenosides [19]. The understanding of the structural modulation of ginsenoside scaffolds may help to develop optimized drug agents for multiple pharmacological and therapeutic adaptogenic effects, with no or minimal complications.

10. Concluding remarks

P. ginseng has been proven as a source of vitality, with a vast range of therapeutic effects, especially in CVD. It has been known to modulate several cellular mechanisms to produce various pharmacological effects. It has presented potential adaptogenic effects on the cardiovascular system by maintaining vascular tone, improving vasomotor function, and balancing blood pressure and vascular endothelial functions.

11. Future perspectives

The current review summarizes the available data on the pharmacological and therapeutic adaptogenic potential of *P. ginseng* and ginsenosides on the cardiovascular system.

- There is a need to evaluate and explore several other mechanistic aspects to confirm *P. ginseng*'s adaptogenic properties on the cardiovascular system.
- A structure–activity relationship is a useful tool in designing the ginsenoside scaffolds to optimize their efficacy and pharmacological use as an adaptogen.
- Future studies could be planned to evaluate the inhibitory effects of ginseng on platelet-related AD progression.
- Furthermore, the neuromodulatory and immunomodulatory effects could be addressed to evaluate the adaptogenic potential of *P. ginseng* and ginsenosides.

Conflicts of interest

All authors have no conflict of interest to declare.

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