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Review Article

Adaptogenic effects of *Panax ginseng* on modulation of cardiovascular functions

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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), neuromodulatory, 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.

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 of 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: Aβ, 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 (Aβ), 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 neuromodulatory 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 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	*In vitro*, *in vivo*	Vasoprotective effects through augmentation of NO signaling by inhibiting arginase	[25]
Total saponin of KRG	*In vivo*	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 antihypotensive effects of *P. ginseng*

Sample	Study type	Results	References
Ginseng extract	*In vivo*	Blood pressure increased	[30]
Ginseng	Human	Blood pressure increased	[31]
Total ginseng saponin	*In vivo*	Enhanced the contractile responses of vascular smooth muscle evoked by phenylephrine and/or KCl through increased extracellular Ca2+ 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

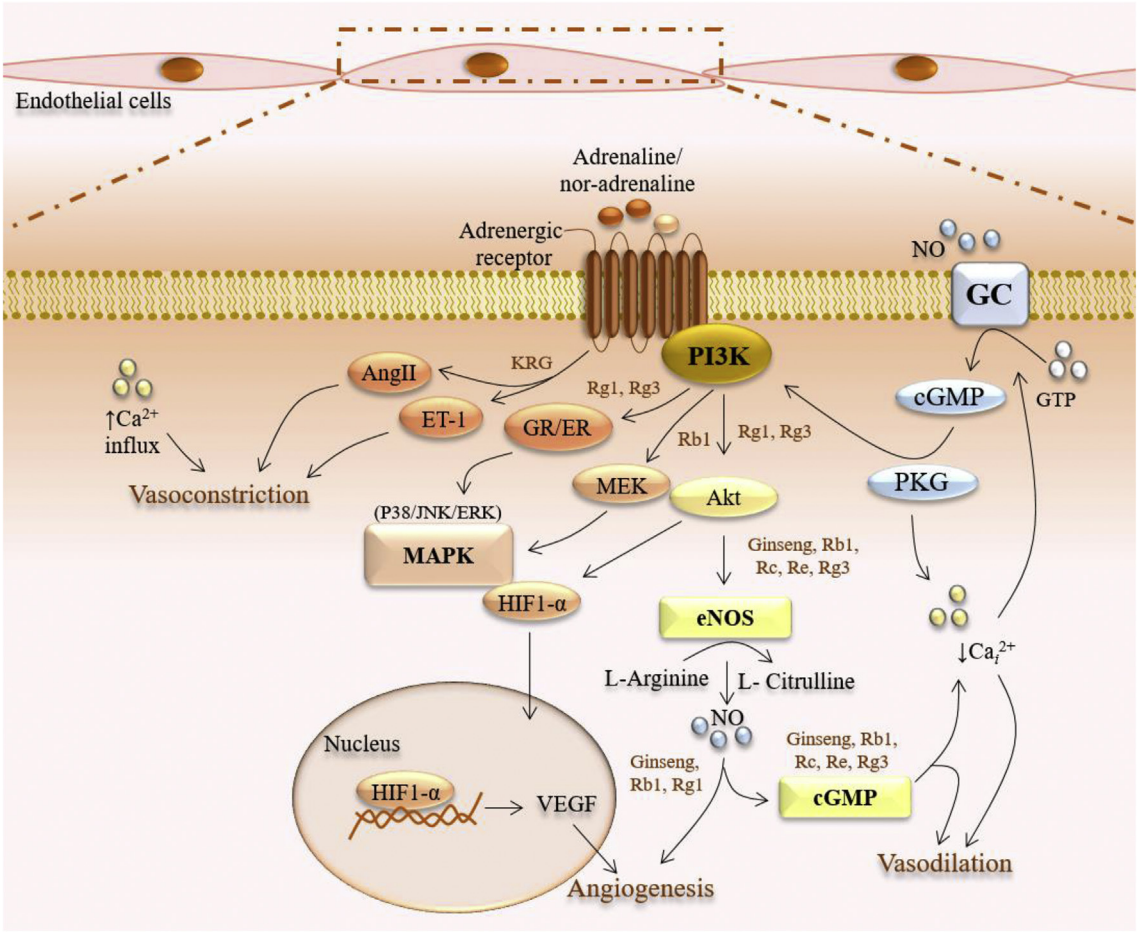

Fig. 1. Effect of *P. ginseng* and ginsenosides on vascular endothelial cells.

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 antihyperlipidemea 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 Aβ 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 Aβ deposition in cerebral blood vessels, and contribute to cerebral amyloid angiopathy in AD [12,71]. Literature shows that Aβ 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 Aβ 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, Rpl, 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, Rpl, 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, Rbl, Rc, Re, Rg3
Rbl, Rc, Re	↑ Antihypertension	↑ Antihypertension	Ginseng, Rbl, 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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References

[1] Brekhman I, Dardymov I. New substances of plant origin which increase nonspecific resistance. Annu Rev Pharmacol 1969;9(1):419–30.
[2] Winston D. Adaptogens: herbs for strength, stamina, and stress relief. Simon and Schuster; 2019.
[3] Panossian AG. Adaptogens: tonic herbs for fatigue and stress. Alternative Compl Ther 2003;9(6):327–31.
[4] Winston D. Harmony remedies: an overview of adaptogens. Washington, NJ: Herbal Therapeutics Research Library; 2004.
[5] Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Després JP, Fullerton HJ, et al. Heart disease and stroke statistics-2016 update: a report from the American heart association. Circulation 2016;133(4). e38-360.
[6] Pagidipati NJ, Gaziano TA. Estimating deaths from cardiovascular disease: a review of global methodologies of mortality measurement. Circulation 2013;127(6):749–56.
[7] Shafiq G, Tatinati S, Ang WT, Veluvolu KC. Automatic identification of systolic time intervals in seismocardiogram. Sci Rep 2016;6:37524.
[8] Gielen S, Landmesser U. The year in cardiology 2013: cardiovascular disease prevention. Eur Heart J 2014;35(5):307–12.
[9] Lim KH, Ko D, Kim J-H. Cardioprotective potential of Korean Red Ginseng extract on isoproterenol-induced cardiac injury in rats. J Ginseng Res 2013;37(3):273.
[10] Smith JN, Negrelli JM, Manek MB, Hawes EM, Viera AJ. Diagnosis and management of acute coronary syndrome: an evidence-based update. J Am Board Fam Med: JABFM 2015;28(2):283–93.
[11] Andrews RK, Berndt MC. Platelet physiology and thrombosis. Thromb Res 2004;114(5–6):447–53.
[12] Donner L, Gremer L, Ziehm T, Gertzen CGW, Gohlke H, Willbold D, Elvers M. Relevance of N-terminal residues for amyloid-beta binding to platelet integrin alphaIIbbeta3, integrin outside-in signaling and amyloid-beta fibril formation. Cell Signal 2018;50:121–30.
[13] Gowert NS, Donner L, Chatterjee M, Eisele YS, Towhid ST, Munzer P, Walker B, Ogorek I, Borst O, Grandoch M, et al. Blood platelets in the progression of Alzheimer's disease. PloS One 2014;9(2). e90523.
[14] Barrett NE, Holbrook L, Jones S, Kaiser WJ, Moraes LA, Rana R, Sage T, Stanley RG, Tucker KL, Wright B, et al. Future innovations in anti-platelet therapies. Br J Pharmacol 2008;154(5):918–39.
[15] Mackman N. Triggers, targets and treatments for thrombosis. Nature 2008;451(7181):914–8.
[16] Grimm Jr RH, Grandits GA, Prineas RJ, McDonald RH, Lewis CE, Flack JM, Yunis C, Svendsen K, Liebson PR, Elmer PJ, et al. Long-term effects on sexual function of five antihypertensive drugs and nutritional hygienic treatment in hypertensive men and women: treatment of Mild Hypertension Study (TOMHS). Hypertension 1997;29(1):8–14.
[17] Badimon L, Vilahur G, Padro T. Nutraceuticals and atherosclerosis: human trials. Cardiovasc Therapeut 2010;28(4):202–15.
[18] Kim J-H. Pharmacological and medical applications of Panax ginseng and ginsenosides: a review for use in cardiovascular diseases. J Ginseng Res 2018;42(3):264–9.
[19] Irfan M, Kim M, Rhee MH. Anti-platelet role of Korean ginseng and ginsenosides in cardiovascular diseases. J Ginseng Res 2020;44(1):24–32.
[20] Lee CH, Kim J-H. A review on the medicinal potentials of ginseng and ginsenosides on cardiovascular diseases. J Ginseng Res 2014;38(3):161–6.
[21] Mohanan P, Subramaniyam S, Mathiyalagan R, Yang D-C. Molecular signaling of ginsenosides Rb1, Rg1, and Rg3 and their mode of actions. J Ginseng Res 2018;42(2):123–32.
[22] Fernandez-Moriano C, González-Burgos E, Iglesias I, Lozano R, Gómez-Serranillos MP. Evaluation of the adaptogenic potential exerted by ginsenosides Rb1 and Rg1 against oxidative stress-mediated neurotoxicity in an *in vitro* neuronal model. PloS One 2017;12(8).
[23] Patel S, Rauf A. Adaptogenic herb ginseng (Panax) as medical food: status quo and future prospects. Biomed Pharmacother 2017;85:120–7.
[24] Nocerino E, Amato M, Izzo AA. The aphrodisiac and adaptogenic properties of ginseng. Fitoterapia 2000;71:S1–5.
[25] Shin W, Yoon J, Oh GT, Ryoo S. Korean red ginseng inhibits arginase and contributes to endotheliumdependent vasorelaxation through endothelial nitric oxide synthase coupling. J Ginseng Res 2013;37(1):64.
[26] Jeon BH, Kim CS, Park KS, Lee JW, Park JB, Kim K-J, Kim SH, Chang SJ, Nam KY. Effect of Korea red ginseng on the blood pressure in conscious hypertensive rats. Gen Pharmacol: Vasc Syst 2000;35(3):135–41.
[27] Vuksan V, Sung M-K, Sievenpiper JL, Stavro PM, Jenkins AL, Di Buono M, Lee KS, Leiter LA, Nam KY, Arnason JT, et al. Korean red ginseng (Panax ginseng) improves glucose and insulin regulation in well-controlled, type 2 diabetes: results of a randomized, double-blind, placebo-controlled study of efficacy and safety. Nutr Metabol Cardiovasc Dis 2008;18(1):46–56.
[28] Qin N, Gong Q-h, Wei L-w, Wu Q, Huang X-n. Total ginsenosides inhibit the right ventricular hypertrophy induced by monocrotaline in rats. Biol Pharm Bull 2008;31(8):1530–5.
[29] Rhee M-Y, Kim Y-S, Bae J-H, Nah D-Y, Kim Y-K, Lee M-M, Kim HY. Effect of Korean red ginseng on arterial stiffness in subjects with hypertension. Journal Alternative Compl Med 2011;17(1):45–9.
[30] Kitagawa H, Iwaki R. Pharmacological study on panax ginseg. Nihon Yakurigaku Zasshi Folia Pharmacologica Japonica 1963;59:348–54.
[31] Siegel RK. Ginseng abuse syndrome: problems with the panacea. Jama 1979;241(15):1614–5.
[32] Chung CH, Hong SP, Cho SH, Hong JG, Lee YK, Lim GH, Yang WH, You HJ, Woo SC, Choi CH, et al. Influence of total ginseng saponin on contractile responses of vasoconstrictors in the isolated rat aorta. Kor Circ J 1999;29(9):976–84.
[33] Chen I-J, Chang M-Y, Chiao S-L, Chen J-L, Yu C-C, Yang S-H, Liu JM, Hung CC, Yang RC, Chang HC, et al. Korean red ginseng improves blood pressure stability in patients with intradialytic hypotension. Evid base Compl Alternative Med 2012;2012.
[34] Park D. Pressor and depressor actions of Panax Ginseng in mammals. Kor Med J 1960;5(85):98. 1960.
[35] Petkov W. Pharmacological studies of the drug Panax ginseng. Mitteilung Arzneim Forschung 1961;11(418):22. 1961.

[36] Wood WB, Roh BL, White RP. Cardiovascular actions of Panax ginseng in dogs. Jpn J Pharmacol 1964;14(3):284–94.
[37] Effect of Korean red ginseng powder (GP), administered orally, on blood pressure in hypertensive rats. In: Sokabe H, Kishi K, Watanabe TX, editors. Proceedings of the ginseng society conference. The Korean Society of Ginseng; 1984.
[38] Kang SY, Schini-Kerth VB, Kim ND. Ginsenosides of the protopanaxatriol group cause endothelium-dependent relaxation in the rat aorta. Life Sci 1995;56(19):1577–86.
[39] Kim ND, Kang SY, Schini VB. Ginsenosides evoke endothelium-dependent vascular relaxation in rat aorta. Gen Pharmacol 1994;25(6):1071–7.
[40] Tousoulis D, Kampoli A-M, Tentolouris Nikolaos Papageorgiou C, Stefanadis C. The role of nitric oxide on endothelial function. Curr Vasc Pharmacol 2012;10(1):4–18.
[41] Hien TT, Kim ND, Pokharel YR, Oh SJ, Lee MY, Kang KW. Ginsenoside Rg3 increases nitric oxide production via increases in phosphorylation and expression of endothelial nitric oxide synthase: essential roles of estrogen receptor-dependent PI3-kinase and AMP-activated protein kinase. Toxicol Appl Pharmacol 2010;246(3):171–83.
[42] Simoncini T, Hafezi-Moghadam A, Brazil DP, Ley K, Chin WW, Liao JK. Interaction of oestrogen receptor with the regulatory subunit of phosphatidylinositol-3-OH kinase. Nature 2000;407(6803):538–41.
[43] Lau W-S, Chan RY-K, Guo D-A, Wong M-S. Ginsenoside Rg1 exerts estrogen-like activities via ligand-independent activation of ERα pathway. J Steroid Biochem Mol Biol 2008;108(1–2):64–71.
[44] Siegel RK. Ginseng and high blood pressure. Jama 1980;243(1):32.
[45] Wang X, Chu S, Qian T, Chen J, Zhang J. Ginsenoside Rg1 improves male copulatory behavior via nitric oxide/cyclic guanosine monophosphate pathway. J of Sex Med 2010;7(2):743–50.
[46] Abdel-Wahhab MA, Joubert O, El-Nekeety AA, Yoon W, Kim Y, Rihn B. Aphrodisiac effects of Panax ginseng extract standardized with ginsenoside Rg3 in male rats. Gen Health Med Sci 2014;1(1):3–8.
[47] De Andrade E, De Mesquita AA, de Almeida Claro J, De Andrade PM, Ortiz V, Paranhos M, Srougi M, Erdogrun T. Study of the efficacy of Korean Red Ginseng in the treatment of erectile dysfunction. Asian J Androl 2007;9(2):241–4.
[48] Kim T-H, Jeon SH, Hahn E-J, Paek K-Y, Park JK, Youn NY, Lee HL. Effects of tissue-cultured mountain ginseng (Panax ginseng CA Meyer) extract on male patients with erectile dysfunction. Asian J Androl 2009;11(3):356.
[49] Toh H. Improved isolated heart contractility and mitochondrial oxidation after chronic treatment with Panax ginseng in rats. Am J Chin Med 1994;22:275–84. 03n04.
[50] Kong H-l, Wang J-p, Li Z-q, Zhao S-m, Dong J, Zhang W-w. Anti-hypoxic effect of ginsenoside Rbl on neonatal rat cardiomyocytes is mediated through the specific activation of glucose transporter-4 ex vivo. Acta Pharmacol Sin 2009;30(4):396–403.
[51] Wang YG, Zima AV, Ji X, Pabbidi R, Blatter LA, Lipsius SL. Ginsenoside Re suppresses electromechanical alternans in cat and human cardiomyocytes. Am J Physiol Heart Circ Physiol 2008;295(2):H851–9.
[52] Bai C-X, 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(1–2):35–44.
[53] Choi S-H, Shin T-J, Lee B-H, Chu D-h, Choe H, Pyo M-K, 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(1–3):138–47.
[54] Kim C-s, Son S-j, Kim H-s, Kim Y-d, Lee K-s, Jeon B-h, Kim KJ, Park JK, Park JB. Modulating effect of ginseng saponins on heterologously expressed HERG currents in Xenopus oocytes. Acta Pharmacol Sin 2005;26(5):551–8.
[55] Jeong D, Irfan M, Kim S-D, Kim S, Oh J-H, Park C-K, Kim HK, Rhee MH. Ginsenoside Rg3-enriched red ginseng extract inhibits platelet activation and *in vivo* thrombus formation. J Ginseng Res 2017;41(4):548–55.
[56] Irfan M, Jeong D, Kwon H-W, Shin J-H, Park S-J, Kwak D, Kim TH, Lee DH, Park HJ, Rhee MH. Ginsenoside-Rp3 inhibits platelet activation and thrombus formation by regulating MAPK and cyclic nucleotide signaling. Vasc Pharmacol 2018;109:45–55.
[57] Irfan M, Jeong D, Saba E, Kwon H-W, Shin J-H, Jeon B-R, Kim S, Kim SD, Lee DH, Nah SY, et al. Gintonin modulates platelet function and inhibits thrombus formation via impaired glycoprotein VI signaling. Platelets 2019;30(5):589–98.
[58] Fan H-Y, Fu F-H, Yang M-Y, Xu H, Zhang A-H, Liu K. Antiplatelet and antithrombotic activities of salvianolic acid A. Thromb Res 2010;126(1):e17–22.
[59] Cho YI, Cho DJ, Rosenson RS. Endothelial shear stress and blood viscosity in peripheral arterial disease. Curr Atheroscler Rep 2014;16(4):404.
[60] Endale M, Lee W, Kamruzzaman S, Kim S, Park J, Park M, Park TY, Park HJ, Cho JY, Rhee MH. Ginsenoside-Rp1 inhibits platelet activation and thrombus formation via impaired glycoprotein VI signalling pathway, tyrosine phosphorylation and MAPK activation. Br J Pharmacol 2012;167(1):109–27.
[61] Yamamoto M, Uemura T, Nakama S, Uemiya M, Kumagai A. Serum HDL-cholesterol-increasing and fatty liver-improving actions of Panax ginseng in high cholesterol diet-fed rats with clinical effect on hyperlipidemia in man. Am J Chin Med 1983;11(1–4):96–101.
[62] Hwang S-Y, Son DJ, Kim I-W, Kim D-M, Sohn S-H, Lee J-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(6):778–83.
[63] Saba E, Jeon BR, Jeong D-H, Lee K, Goo Y-K, Kim S-H, Sung CK, Roh SS, Kim SD, Kim HK, et al. Black ginseng extract ameliorates hypercholesterolemia in rats. J Ginseng Res 2016;40(2):160–8.
[64] Kwak Y-S, Kyung J-S, Kim JS, Cho JY, Rhee M-H. Anti-hyperlipidemic effects of red ginseng acidic polysaccharide from Korean red ginseng. Biol Pharm Bull 2010;33(3):468–72.
[65] In G, Ahn N-G, Bae B-S, Lee M-W, Park H-W, Jang KH, Cho BG, Han CK, Park CK, Kwak YS. *In situ* analysis of chemical components induced by steaming between fresh ginseng, steamed ginseng, and red ginseng. J Ginseng Res 2017;41(3):361–9.
[66] Laclaustra M, Corella D, Ordovas JM. Metabolic syndrome pathophysiology: the role of adipose tissue. Nutr Metabol Cardiovasc Dis 2007;17(2):125–39.
[67] Morrison CD, Huypens P, Stewart LK, Gettys TW. Implications of crosstalk between leptin and insulin signaling during the development of diet-induced obesity. Biochim Biophys Acta (BBA)-Mol Basis Dis 2009;1792(5):409–16.
[68] Venancio JC, Margatho LO, Rorato R, Rosales RRC, Debarba LK, Coletti R, Antunes-Rodrigues J, Elias CF, Elias LLK. Short-term high-fat diet increases leptin activation of CART neurons and advances puberty in female mice. Endocrinology 2017;158(11):3929–42.
[69] Kwak Y-S, Kyung J-S, Wee J-J. Anti-obesity activity of red ginseng acidic polysaccharide from Korean red ginseng (Panax ginseng CA Meyer). Adv Complement Alt Med 2019;42(2):1–10.
[70] Dıez JJ, Iglesias P. The role of the novel adipocyte-derived hormone adiponectin in human disease. Eur J Endocrinol 2003;148(3):293–300.
[71] Gowert NS, Donner L, Chatterjee M, Eisele YS, Towhid ST, Münzer P, Walker B, Ogorek I, Borst O, Grandoch M. Blood platelets in the progression of Alzheimer's disease. PloS One 2014;9(2).
[72] Casoli T, Balietti M, Giorgetti B, Solazzi M, Scarpino O, Fattoretti P. Platelets in Alzheimer's disease-associated cellular senescence and inflammation. Curr Pharmaceut Des 2013;19(9):1727–38.
[73] Shen MY, Hsiao G, Fong TH, Chen HM, Chou DS, Lin CH, Sheu JR, Hsu CY. Amyloid beta peptide-activated signal pathways in human platelets. Eur J Pharmacol 2008;588(2–3):259–66.
[74] Kokjohn TA, Van Vickle GD, Maarouf CL, Kalback WM, Hunter JM, Daugs ID, Luehrs DC, Lopez J, Brune D, Sue LI, et al. Chemical characterization of pro-inflammatory amyloid-beta peptides in human atherosclerotic lesions and platelets. Biochim Biophys Acta (BBA)-Mol Basis Dis 2011;1812(11):1508–14.
[75] Davies TA, Long HJ, Eisenhauer PB, Hastey R, Cribbs DH, Fine RE, Simons ER. β amyloid fragments derived from activated platelets deposit in cerebrovascular endothelium: usage of a novel blood brain barrier endothelial cell model system. Amyloid 2000;7(3):153–65.
[76] Lee S-T, Chu K, Sim J-Y, Heo J-H, Kim M. Panax ginseng enhances cognitive performance in Alzheimer disease. Alzheimer Dis Assoc Disord 2008;22(3):222–6.
[77] Wang Y, Liu J, Zhang Z, Bi P, Qi Z, Zhang C. Anti-neuroinflammation effect of ginsenoside Rbl in a rat model of Alzheimer disease. Neurosci Lett 2011;487(1):70–2.
[78] Ong W-Y, Farooqui T, Koh H-L, Farooqui AA, Ling E-A. Protective effects of ginseng on neurological disorders. Front Aging Neurosci 2015;7:129.
[79] Chen X. Cardiovascular protection by ginsenosides and their nitric oxide releasing action. Clin Exp Pharmacol Physiol 1996;23(8):728–32.
[80] Nag SA, Qin J, Wang W, Wang M-H, Wang H, Zhang R. Ginsenosides as anticancer agents: *in vitro* and *in vivo* activities, structure-activity relationships, and molecular mechanisms of action. Front Pharmacol 2012;3:25.
[81] Yang Q, Wang N, Zhang J, Chen G, Xu H, Meng Q, Du Y, Yang X, Fan H. *In vitro* and in silico evaluation of stereoselective effect of ginsenoside isomers on platelet P2Y12 receptor. Phytomedicine 2019;64:152899.
[82] Azike CG, Charpentier PA, Hou J, Pei H, Lui EMK. The Yin and Yang actions of North American ginseng root in modulating the immune function of macrophages. Chin Med 2011;6(1):21.