



Cardiovascular effects of panax ginseng

Panax ginseng'in kardiyovasküler etkileri

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Abstract

Cardiovascular Diseases (CVD), being present in 400 million people across the globe in people of all races, ages and genders is amongst the more important types of diseases present in the World Health Organizations' "2013-2020 Global Action Plan for the Prevention and Control of Non-communicable Diseases". CVD are the leading cause of death in the World as well as in Turkey. Ginseng, also known as *Panax ginseng* root, is widely used in Turkey to prevent tiredness, fatigue, and loss of concentration, to improve mental and physical capacity during recovery period, as well as to reduce the degenerative effects of stress. It also acts as adaptogen due to its anti-stress effect while regulating blood sugar in diabetic patients and increasing erectile capacity and libido in cases with erectile dysfunction. In addition, use of Ginseng as a dietary supplement is increasing day by day among individuals with cardiovascular risk factors such as hypertension, hypercholesterolemia, and oxidative damage. In the literature, there is controversial data concerning *Panax ginseng's* pharmacological activity on the cardiovascular system. Increasing the synthesis of nitric oxide, it is observed that Ginseng has both hypertensive and hypotensive effects. While it is stated that dietary supplements containing Ginseng affect the autonomic nervous system, but also increases the blood pressure, reduces or making no change, controversial results were obtained. For these conflict data, ginsenoside, first reducing and then increasing the blood pressure, is thought to be responsible. Depending on the acute and chronic use of Ginseng, it has also been observed that various pharmacological activities exist. In this review, we aim to present the cardiovascular effects of Ginseng.

Keywords: Alternative Medicine; Cardiovascular System; *Panax ginseng*.

Öz

Dünyada farklı ırk, yaş ve cinsiyetten yaklaşık 400 milyon insanda görülen kardiyovasküler hastalıklar (KVH), Dünya Sağlık Örgütü'nün "Bulaşıcı Olmayan Hastalıklar 2013-2020 Eylem Planı" içerisinde yer alan önemli bir hastalık grubudur. KVH'nın neden olduğu ölümler dünyada ve ülkemizde ilk sıradadır. Ülkemizde "Ginseng" olarak bilinen *Panax ginseng* bitkisinin kökleri yorgunluk, bitkinlik, konsantrasyon kaybı gibi durumlarda, iyileşme dönemlerinde mental ve fiziksel kapasitenin artırılmasında, anti-stres etki ile adaptöjen olarak davranıp vücutta stresin oluşturduğu dejeneratif etkilerin azaltılmasında, diyabetik hastalarda kan şekerinin düzenlenmesinde, erektil disfonksiyonlu olgularda ereksiyon kapasitesinin ve libidonun artırılmasında tıbbi olarak kullanılmaktadır. Ayrıca hipertansiyon, hiperkolestrolemi ve oksidatif hasar gibi kardiyovasküler risk faktörleri bulunan bireyler arasında Ginseng'in gıda takviyesi olarak kullanımı gün geçtikçe artmaktadır. Literatürde *Panax ginseng*'in kardiyovasküler sistem üzerindeki farmakolojik etkinliğiyle ilgili tartışılmalı veriler mevcuttur. Ginseng'in nitrik oksit sentezini artırarak hem hipertansif hem de hipotansif etki gösterdiği gözlenmiştir. Ginseng içeren gıda takviyelerinin otonom sinir sistemini etkileyerek kalp hızını azalttığı belirtilirken; aynı zamanda kan basıncını artırdığı, azalttığı veya kan basıncında herhangi bir değişiklik yapmadığı yönünde tartışılmalı bulgular elde edilmiştir. Bu çelişkili verilerden, kan basıncını önce azaltıp daha sonra artırarak bifazik aktivite gösteren ginsenositlerin sorumlu olduğu düşünülmektedir. Ayrıca akut ve kronik Ginseng kullanımına bağlı olarak çeşitli farmakolojik aktivite farklılıkları olduğu gözlenmiştir. Bu yazıda Ginseng'in kardiyovasküler etkilerini sunmayı amaçladık.

Anahtar Kelimeler: Alternatif Tıp; Kardiyovasküler Sistem; *Panax ginseng*.

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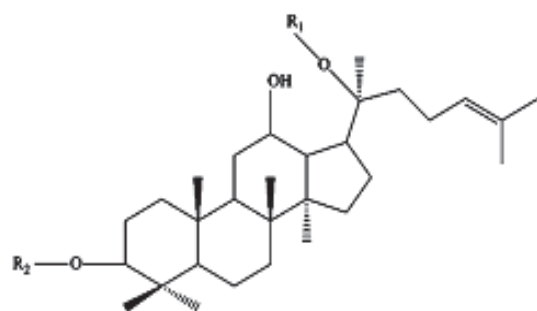
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Cardiovascular diseases (CVD) are usually characterised by vascular dysfunction as a result of atherosclerosis, thrombosis and high blood pressure (1). The fact that heart diseases, especially with myocardial ischemia (MI) in the lead, are the primary cause of death of people of all ages is the main reason behind long-term researches on CVD (2). CVDs such as peripheral vascular disease, coronary artery disease, heart failure, dyslipidemia, and hypertension are seen in 400 million people in the world of different races, ages and gender (3). Early diagnosis is of utmost important in the prevention and treatment of disease (4).

Containing indications in terms of treatment of human health, herbal medicines can be used in pharmacotherapy as long as they provide parameters related to quality, safety, and efficacy as in conventional drugs (5). After the control of the correct use of herbal treatment modalities with the publication of regulations concerning "Traditional and Complementary Medicine Practices" in the Official Gazette (issue number 29158) on 27 October 2014, use of of natural products in rational treatment modalities has been increasing day by day (6). In recent years, there are publications in the literature about undesirable situations taking place due to use of herbal medicine (3).

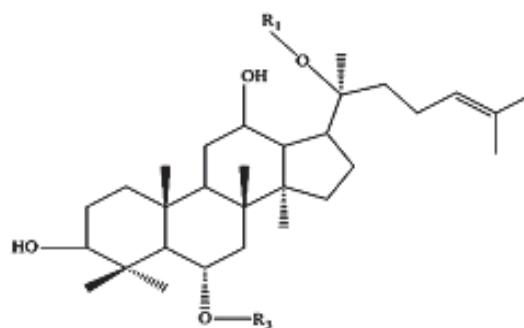
As a part of the Traditional and Complementary Medicine Practices, the use of Panax ginseng has become widespread among individuals, especially in women, the educated, and in patients who believe that they have received inadequate treatment. Used as a food supplement in the western medicine practice, the ginseng root is becoming more widely used as an alternative to conventional applications among patients with cardiovascular risk factors such as hypertension, hypercholesterolemia, and oxidative damage (2). Main Panax types under the trade name "Ginseng" available on the market are *P. ginseng* (Korean ginseng), *P. quinquefolius* (American ginseng), and *P. notoginseng*. *P. ginseng* is naturally grown and traditionally used among the people in the Far East, particularly in China, Korea and Japan. Known as "Ginseng" in Turkey, this plant is also known as Asian ginseng, Korean ginseng, or Chinese ginseng (1, 7).

The main components of Panax species are saponins and polysaccharides in dammarane, ocotillo, and oleana structure (2). Due to the total ginsenosides, protopanaxadiol (PPD) and protopanaxatriol (PPT) ratio as well as some leading ginsenosides found in it, *P. ginseng* differs from other Panax species. *P. ginseng* contains more amounts of ginsenosides Rg1 and Rg2 (Figure 1) (8).



Ginsenosides	R ₂	R ₁
Rb1	Glc ¹⁻³ Glc-	Glc ¹⁻⁶ Glc-
Rb2	Glc ¹⁻³ Glc-	Ara(p) ¹⁻⁶ Glc-
Rc	Glc ¹⁻³ Glc-	Ara(f) ¹⁻⁶ Glc-
Rd	Glc ¹⁻³ Glc-	Glc-

(A) Protopanaxadiol Structure



Ginsenosides	R ₃	R ₁
Rg1	Glc-	Glc-
Rc	Rha ¹⁻³ Glc-	Glc-

(B) Protopanaxatriol Structure

Figure 1. Molecule structure of ginsenosides: (A) Protopanaxadiol (PPD) formation: Rb₁, Rb₂, Rc and Rd; (B) Protopanaxatriol (PPT): Rg₁ and Re (9).

Because of the individual differences in terms of bacteria naturally found in the intestinal flora, bioactive metabolites vary. These metabolites can be easily absorbed in the gastrointestinal system and they are pharmacologically active and nonpolar compounds. To avoid these differences, ginseng

preparations are introduced to the market after being fermented by enzymes and microorganisms (2).

Ginsenosides are generally known to be responsible for the pharmacological effects of ginseng; and because ginseng extracts contain many different ginsenosides while each ginsenoside may have many

effects on a single tissue, ginseng use bears different and variable results. As a result of the different chemical structures, ginsenosides have various mechanisms and pharmacological effects. This plant, including its roots, is used in many different ways such as recovering from fatigue, exhaustion, and loss of concentration; increasing mental and physical capacity in the recovery period; reducing degenerative effects of stress in which ginseng acts like an adaptogen with anti-stress effect; regulating blood sugar in diabetics patients, and enhancing erection and libido in individuals with erectile dysfunction. Ginseng and the ginsenosides it contains are reported to have vasorelaxant, antioxidant, anti-inflammatory, and anticancer activities. Ginsenosides are also reported to have effect on the central and peripheral nervous system by having a long-term impact during the transition from illness to health status (2, 10).

Panax ginseng Related Cardiovascular Research

As indicated in the 2011 study by Kim and Park, more than half (57%) of the studies on Panax types are pharmacodynamic studies on *P. ginseng*. According to this study, the number of studies on ginseng in many countries in Europe (including Turkey), North America, and Central Asia has increased recently (Figure 2) (11, 12).

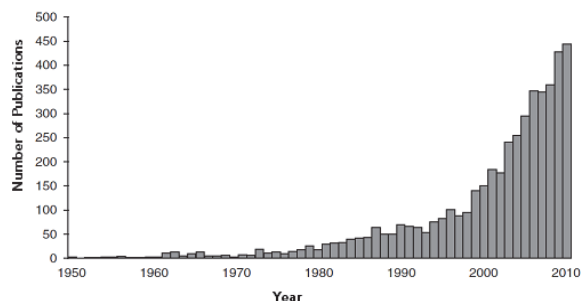


Figure 2. The search results for the keywords "ginseng" and "ginsenoside" between 1950 and 2010 on Pubmed database and the distribution of these publications in years (12).

With its active ingredients, ginseng displays several pharmacological activities due to its various effect mechanisms. Ginsenosides inhibit the formation of reactive oxygen species (ROS), increase nitric oxide (NO) production and blood circulation, improves vasomotor tone, and regulate blood lipid profiles (2).

In their study evaluating the effects of ginseng on patients who underwent mitral valve surgery, Zhan et. al have compared intraoperative transesophageal ECO with pre- and post-operative cardiac functions and have determined the structure of myocardial cells by electron microscope. In this study, total ginsenosides and ginsenoside Rb are reported to have a protective effect against myocardial ischemia-

reperfusion (IR) damage in open heart surgery. These researchers have reported that endovascular therapy has received much appreciation in treating certain types of CVD (13).

Ding et al. have claimed that ginseng has positive effects on hemodynamic and biochemical parameters in patients with congestive heart failure (CHF). In this study, ginseng-digoxin combination is reported to have a synergistic effect in the treatment of CHF while ginseng has proved to be an effective and safe adjuvant with no significant side effects (14). Wu et al. have shown the ginsenosides found in the ginseng extract to have preventive effects on neointimal formation in rats that underwent percutaneous transluminal coronary angioplasty. However, this activity has not yet been tested clinically (15).

Clinical trials for the treatment of hypertension have shown that ginseng reduces atherosclerosis formation and provides therapeutic benefit by increasing cardiac function. According to the study by Caron et al., the QTc interval, one of the hemodynamic parameters in electrocardiogram, is prolonged while diastolic blood pressure decreases in healthy subjects taking ginseng orally (16).

It has been reported that Red Ginseng extract improves coronary flow reserve and increases the number of various angiogenic cells within the flow in patients with acute MI. By considering all these results together, it has been emphasised that ginseng improves blood circulation by inhibiting platelet aggregation and coagulation (17).

Some of the pharmacological effects of ginseng on vascular endothelial cells have been scientifically proven. Research has shown that aqueous extract of Red Korean ginseng may play a role in angiogenesis by activating kinase 1/2 and eNOS pathways, which regulate PI3K/Akt-dependent extracellular signalling in human umbilical endothelial cells while ginsenosides may show angiomodulator and neurological effects (18). Through Re, PI3K/Akt, and NO pathways, ginsenosides activate K⁺ channels in smooth vascular muscle cells (19). Evaluating all these observations together, it has been put forward that ginseng saponins have protective effects on vascular endothelial cells by way of cellular stimulation (Figure 3) (2, 20).

Ginseng's pharmacological effect against oxidative damage has been scientifically proven. It has also been put forward that ginseng and ginsenosides show antioxidant activity by inhibiting the increase in free harmful radicals and lipid peroxidation (2). Ginsenosides have protective effect against deterioration of the properties of the erythrocyte membrane due to Rg1 and Rh2 oxidation (21). Ginseng also prevents the potential damage ROS can

cause through NO secretion. Rb1 and other ginsenosides stop ROS productivity and block endothelial dysfunction stimulated by homocysteine and HIV protease inhibitors. By improving internal antioxidant enzymes and acting as free radical scavenging agents, ginsenosides display antioxidant effects (22, 23). Consequently, by preventing the onset of ROS, ginseng is able to inhibit oxidative damage (2).

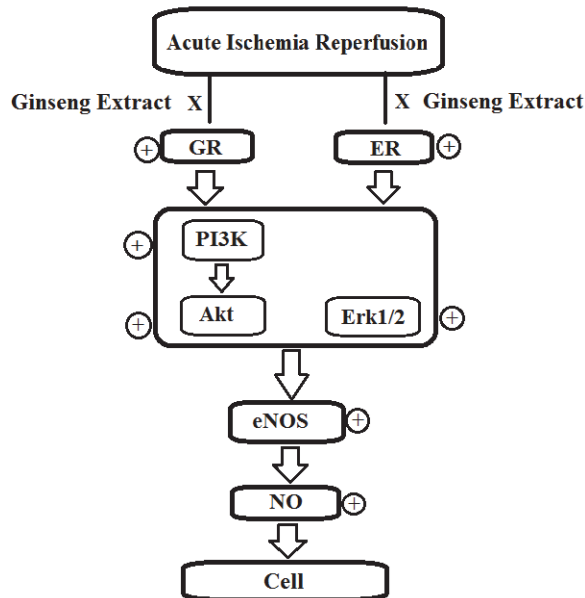


Figure 3. The cardio-protective effect of P. Ginseng extract on acute ischemia reperfusion damage (20).

There are reports about the antihyperlipidemic effects of polysaccharides, which are found in the red Korean ginseng in acidic nature (24). It has been noted that ginsenoside Rd compound prevents atherosclerosis in mice (25). It has also been discussed that ginseng can regulate blood lipid profiles (2).

Panax Ginseng Related Cardiovascular Case Reports in the Literature

Reports show that panax ginseng may cause mild toxicity and have side effects in humans. By regularly applying ginseng orally to 133 patients for 2 years, Siegel has identified unwanted symptoms of ginseng use and concluded that 17% of the patients had hypertension while approximately 10% of the patients had hypotension. These adverse effects have been associated with application of high doses for a long time (26). In two of the randomised controlled studies investigating the effects of multiple dose of ginseng on blood pressure, it was observed that ginseng reduces blood pressure significantly compared to placebo. Again, in two of the studies investigating the effects of single dose of ginseng on blood pressure, ginseng was reported to reduce

systolic and diastolic blood pressure to a great extent (by 8-11%). Other studies indicate that ginseng brings about insignificant decrease (by 1-4%) in blood pressure (27).

In a prospective, randomised, double-blind, and placebo-controlled study, the results of 30 cases, who were given 200mg of P. ginseng extract or placebo for 28 days, were recorded in groups. Throughout the study, ECG and blood pressure of subjects who were administered these drugs for 1 day or 28 days were measured after 50 minutes, 2 hours, and 5 hours. At the end of the first day, a prolongation of QTc interval as well as decrease in diastolic blood pressure were observed in healthy subjects within 2 hours of 200mg of single dose ginseng extract. However, these observations were not found to be clinically significant (16). Another case report presents the case of a 43-year-old healthy female patient with no cardiovascular risk factors who developed torsades de pointes (prolonged QT) after a regular daily use of P. ginseng for six months (28). In another study investigating the relationship between the use of ginseng in renal diseases and cardiovascular side effects, it was reported that a 83-year-old woman with chronic kidney failure developed bradycardia and atrial fibrillation after using ginseng for 1 week (29). A 64-year-old male patient with no previous findings of hypertension was reported to develop ischemic attack (amaurosis fugax) and hypertensive crisis (195/95 mmHg) after using Ginseng Forte-Dietista that contains 500mg of P. ginseng for 13 days. A week later, after discontinuing ginseng use, his level of blood pressure decreased back to the starting (<140/90 mmHg) level. It was in this study that P. ginseng was reported to trigger hypertensive crisis, which is a temporary ischemic attack also known as amaurosis fugax, for the first time (30).

A survey covering 34 publications on the effect of food supplements containing ginseng on cardiovascular risk factors has highlighted that current data is not sufficient or competent to support the use of ginseng as herbal medicine (27). It was indicated that more studies throwing light on ginseng's pharmacokinetic and pharmacodynamic profile are needed to determine whether the relationship between ginseng use and changes in blood pressure is simply random as well as to see if ginseng triggers amaurosis fugax (31).

Panax Ginseng Related Cardiovascular Case Reports from Turkey

There are some case reports from Turkey concerning patients using a drug sold under the name Clavis Panax (CP), which contains P. ginseng, bindii (Tribulus terrestris), and oats (Avena sativa). The case reports related to the use of this product, which include the onset of atherosclerosis (2), sudden INR elevations

(2), cardiogenic shock due to acute anterior myocardial infarction (1), stent thrombosis (3), and acute diffuse pulmonary embolism (1), are presented below.

In their 2012 study, Turfan et al. report the case of two patients who were using warfarin due to aortic valve replacement and atrial fibrillation and were hospitalised because of very high INR values at routine checkups. It was learnt that the patients were using a herbal product under the name of CP for the last month. In neither of the patients, there were no other agents that could cause interaction nor a change in diet. With no observed active bleeding, both patients were discharged after discontinuing CP and re-adjusting warfarin doses (32). One of the reports from 2012 presents the case of a patient who had intermittent chest pain, refused coronary angiography that was recommended by cardiologists, and presented at the emergency department with extensive anterior MI and cardiogenic shock after starting using CP. The 65-year-old diabetic male patient was taken to the operating theatre for primary percutaneous coronary intervention procedures 3 hours into the onset of pain. Ejection fraction was measured as 40% on echocardiographic examination; there were also apex, interventricular septum, and hypo-kinetic anterior. After planning his medical treatment, the patient was discharged (33). In the 2012 case report by Vatankul et al. are presented 3 cases with coronary stents who were diagnosed with acute coronary syndrome while using CP along with antiplatelet therapy. In the coronary angiography of all three patients, who presented with chest pain, it was observed that stents were almost fully blocked. The obstruction in the stents were cleared away fully after applying balloon procedure. It was learnt that all three patients had been using CP alongside dual antiplatelet therapy for the last three months. Patients were advised to avoid using this herbal mixture with dual antiplatelet therapy and were discharged. There were no reported problems in their four-month follow-ups (34). Yuksel et al.'s case report published in 2013 reports the case of an acute pulmonary embolism related to the use of a herbal mixture on the market under the name of CP. In this report, a 41-year-old male patient, who was using CP, was admitted to the emergency room with sudden onset of shortness of breath and syncope. After the tests (blood gas, echocardiography, ventilation-perfusion scintigraphy), the patient was diagnosed with acute diffuse pulmonary embolism. The patient was applied thrombolytic therapy and dyspnea was reported to have improved (35). Atar et al.'s 2012 case report presents the case of two patients who underwent primary percutaneous coronary intervention (PCI) after being admitted with acute inferior myocardial infarction. The patients were re-admitted with non-ST-elevated MI and it was seen that the expected atherosclerotic progression

was accelerated, that there was rapidly developing restenosis in the intracoronary metal stents, and that there was a swift progress in a very short time in atherosclerotic plaques in coronary arteries which were not operated. It was learnt that the patients had been continuing the recommended drug treatment although they had also been using CP outside the recommendations of doctors after PCI. Although there are experimental studies on each individual substance in CP, it was reported that there is no scientific report on the effects of the combination of these substances (36).

In a study evaluating the in vivo and in vitro studies, clinical trials, and case reports on the toxicity, reliability, and other side effects of ginseng, it was stated that patients abusing the use of ginseng may develop affective disorders, allergies, cardiovascular and renal toxicity, vaginal bleeding, gynecomastia, hepatotoxicity, hypertension, reproductive toxicity, and interactions with anticoagulant drugs. The same study also claims that there is need to conduct more research to have a better understanding of the risky conditions that can be seen in people abusing ginseng (31).

Studies have shown that ginseng, which is used as a food supplement for therapeutic purposes, shows a wide range of activities during physiological and/or pathological processes related to CVD. It is shown that it can accelerate atherosclerosis and can lead to a pro-thrombotic pictures in patients with hypertension, diabetes, hyper-lipidemia, and coronary artery disease. The impact mechanism of ginseng and its compounds on CVD is not yet fully understood. Moreover, it has been stated that use of herbal mixtures, drug interactions and side effects of which are not fully known, may potentially serious consequences and that further research on such drugs is needed. In order to better understand the cardiovascular effects of preparations containing ginseng, there is need for more structure-activity, pharmacokinetic, and toxicity studies as well as for therapeutic studies with human and animal models.

We believe that this review will contribute to further studies on the cardiovascular effects of Panax ginseng.

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