

Pharmaceutical And Medicinal Applications Of Panax Ginseng And Ginsenosides And Their Theuropatic Role In Different Disease

Ihteshamul haq¹, Seher Obaid², Rubina Salma Yasmin³, munaza khattak⁴, Amber javaid⁵, Muhammad Abbas⁶, Mohsina Haq⁷, Faheem Anwar¹

¹Department of Biotechnology and Genetic Engineering Hazara University Mansehra Kp Pakistan.

²Department of Physiology Northwest School of Medicine .

³Forensic Medicine and Toxicology Peshawar medical college Riphah international university Islamabad.

⁴Department of physiology Peshawar Dental College, Riphah international university Islamabad.

⁵Department of pharmacology Peshawar medical college, Riphah international university Islamabad.

⁶Department of Medicine PRIME hospital Peshawar medical college Warsak road Peshawar Kp Pakistan.

⁷Department of microbiology Peshawar medical college. Riphah international university.

Corresponding Author: Mohsina Haq⁷, Co-Corresponding Author: Faheem Anwar¹

Abstract

Panax ginseng, also called Asian or Korean ginseng, has long been traditionally used in Korea and China to treat various diseases. The major active ingredients of P. ginseng are ginsenosides, which have been shown to have a variety of therapeutic effects, including antioxidation, antiinflammatory, vasorelaxation, antiallergic, antidiabetic, and anticancer. To date, approximately 40 ginsenoside components have been reported. Current review is concentrating on using a single ginseng compound, one of the ginsenosides, instead of the total ginseng compounds, to determine the mechanisms of ginseng and ginsenosides. Recent in vitro and in vivo results show that ginseng has beneficial effects on cardiac and vascular diseases through efficacy, including antioxidation, control of vasomotor function, modulation of ion channels and signal transduction, improvement of lipid profiles, adjustment of blood pressure, improvement in cardiac function, and reduction in platelet adhesion. This review aims to provide valuable information on the traditional uses of ginseng and ginsenosides, their therapeutic applications in animal models and humans, and the pharmacological action of ginseng and ginsenosides.

Keywords. Blood pressure, lipid profile, myocardial protection, Panax ginseng,

Introduction

Panax ginseng is one of the most commonly greatly used species of ginseng. For thousands of years, this species, which is native to Korea, China, and Japan, has been an important cure in traditional medicine, where it has been used mainly as a remedy for spiritlessness and fatigue. [1] The name Panax means "all healing" and stemmed from the traditional confidence that ginseng can cure all illness of the human body. The main active components in P. ginseng are ginsenosides, which are triterpen saponins. Most research on the pharmacological and medicinal functions of P. ginseng has focused on ginsenosides. [2] Panax ginseng was first cultivated around 11 BC and has a medical history of more than five thousand years. The genus name of Panax ginseng "Panax" was given by the Russian botanist C.A. Meyer, and it is derived from the Greek words "pan" meaning all and "axos" meaning cure. The species name "ginseng" comes from the Chinese word "rensheng" which means "human" as ginseng roots resemble the human body [3] Ginseng is a widespread herbal medicine and it has served as an important component of many Chinese and Korean prescriptions since thousands of years and Today it still occupies a permanent and prominent position in the herbal (best-sellers) list and is considered the most widely taken herbal product in the world [4] Moreover, it is estimated that more than six million Americans are regularly consuming ginseng products. Ginseng is believed not only to engender physical benefits, but also to have positive effects on cognitive performance and wellbeing.[5] Among the ginseng species, P. ginseng (Korean ginseng), Panax notoginseng (Chinese ginseng), Panax japonicum (Japan ginseng), and Panax guinguefolius (American ginseng) are the most common. A lot of research has focused on individual ginsenosides instead of whole ginseng against many disease conditions.^[6] among these ginsenosides, Rb1, Rg1, Rg3, Re, and Rd are most often studied [7] The ginsenoside content of ginseng is varying depending on the Panax species, the plant age, the part of the plant, the preservation method, the season of harvest, and the extraction method [8] Cardiovascular disease is the major cause of morbidity and mortality and includes various diseases such as vascular disease, heart failure, coronary artery disease, cardiac ischemia, and hypertension [9] Cardiac risk factors, such as cigarette smoking, increased low-density lipoprotein cholesterol, decreased level of high-density lipoprotein cholesterol, diabetes, and hypertension, are the main causes of cardiovascular disease [10]]. Many researchers have shown that inflammation of blood vessels can result in atherosclerosis and coronary artery dysfunction [11] endothelial injury of blood vessels can be initiated by dangerous factors involved in cardiovascular disease [12] . Inflammation within the arterial wall is established by many cytokines, interleukins, and free radicals such as reactive oxygen species (ROS) [13] nowadays herbal medicine has received much attention and is recommended as a

natural alternative to maintain one's health. Therefore, we try in this review to focus on the recently reported medicinal effects of ginseng and to summarize the results of different scientific studies using ginseng particularly in cardiovascular diseases.

General effects of ginseng

Ginseng products are usually used as a general tonic and adaptogen to help the body to resist the adverse influences of a wide range of physical, chemical, and biological factors and to restore homeostasis [14] These tonic and adaptogenic effects of ginseng are believed to enhance physical performance (including sexual function) and general vitality in healthy individuals, to increase the body's ability to fight stress in stressful circumstances, and to support resistance to diseases by strengthening normal body function as well as to reduce the detrimental effects of the aging processes [15].

Ginsenosides are the pharmacologically active components in ginseng

Ginseng contains many active constituents, of which ginsenosides are very important. About 200 ginsenosides have been reported, including major ginsenosides (Rb1, Rb2, Rc, Rd, Re, Rg1, etc.) and minor ginsenosides (Rg3, Rh1, Rh2, etc.) [16] By chemical structure, ginsenosides are classified into two major groups, protopanaxadiol (PD) and protopanaxatriol (PT), which share a four-ring hydrophobic steroid-like structure with sugar moieties, but differ in the carbohydrate moieties at C3, C6, and C20 (Fig. 1) [17] To date, over 30 ginsenosides have been reported and classified into the two categories (1) the 20(S)-PD (ginsenosides Rb1, Rb2, Rb3, Rg3, Rh2, Rc, Rd, and Rs1) and (2) the 20(S)-PT (ginsenosides Rg1, Rg2, Rh1, Re, and Rf). The difference between PD and PT groups is the presence of a carboxyl group at the C6 position of PD. [18]

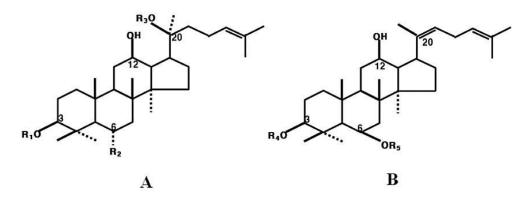


Fig 1. Molecular Structure of Protopanaxadiol and Protopanaxatriol of ginsenosides

Red ginseng, which results from the special preparation of ginseng, has an unusual saponin profile, with ginsenosides Ra1, Ra2, Ra3, Rf2, Rg4, Rg5, Rg6, Rk1, Rs1, and Rs2 likely being the results of stem transformation and deglycosylation of naturally generated ginsenosides [19]

These compounds can confirm the traditional knowledge that red ginseng is of higher pharmacological and medicinal functions than white ginseng [20]

Cognitive effects of ginseng

The use of herbal medicine, particularly ginseng, for improving cognitive performance has become increasingly popular during recent years and some studies have shown its enhancing effects on learning and memory either in aged and/or brain damaged rodents. [21] The ginseng extract powder had significant effects on neurological and psychiatric symptoms in aged humans and psychomotor functions in healthy subjects, respectively. This positive effect of ginseng on cognition performance is due to the direct action of ginseng on the hippocampus,[22] The influence of ginsenoside Rg1 on the proliferating ability of neuronal progenitor cells may serve as an important mechanism underlying its nootropic and antiaging effects particularly on learning and memory [23]

Ginseng and ginsenosides improve antioxidant and blood circulation

Ginseng has antioxidative, vasorelaxation, anti-inflammatory, and anticancer activities [24] In addition, ginseng is also widely used to address cardiovascular risk factors such as hypertension and hypercholesterolemia. Cardiac ischemia can be induced by myocardial damage through the production of ROS; however, ginseng and ginsenosides have been shown to improve the coronary blood flow. [25] Ginsenosides inhibited myocardial injury through the increment of 6-keto-prostaglandin F1 α and decreases of lipid peroxidation [26] Ginsenoside Re is a strong antioxidant that conserves cardiomyocytes against oxidation via its free radical scavenging properties. Also, ginsenoside Re might play a primary role in an antioxidative effect to increase cardiomyocytes survival and cardiac contraction under cardiac ischemia [27] the ginsenoside Re has an antioxidant action, protecting cardiac cells from oxidative damage, and that these protective effects can be mostly attributed to scavenging of free radicals.[28] ginseng prevented ROS production through the stimulation of nitric oxide. Ginsenoside-Rb1 and other ginsenosides blocked endothelial dysfunction induced by homocysteine through the inhibition of ROS production [29].

Ginseng and ginsenosides improve cardiac function

Cardiovascular disease (CVD) is an important problem among the 400 million indigenous populations around the world, and has been included in the World Health Organization '2008-2013 Action plan for non communicable diseases [30] 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 [31] 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 [32] 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 sub endothelial space and also Different Environmental and Genetic factor cause cardiovascular disease. (Fig 2) [33]

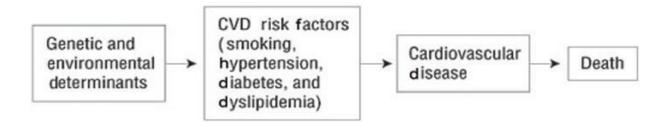


Fig 2. Pathway relating cardiovascular disease (CVD) mortality. The established CVD risk factors lie in the middle of a chain of events that leads to cardiac death

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.[34] Ginsenosides protect the heart against cardiotoxicity induced by doxorubicin and inhibit the cardiac hypertrophy induced by monocrotaline in a rat model [35] Ginsenoside Rg1 protected against left ventricular hypertrophy caused by aorta coarctation produced through nitric oxide production [36] ginsenoside Rg1 decreased left ventricular hypertrophy, and P. ginseng inhibited apoptosis in cardiomyocytes by modulating Bcl-2 and caspase-3 during ischemia and reperfusion [37] ginsenoside Rg1 protected cardiomyocytes from oxidative injury through antioxidative effects and calcium modulation [38] the ginseng inhibited cardiac hypertrophy and heart failure through Nhe-1 modulation and decrease of calcineurin activation [39] In the heart, calcium ion (Ca2+) is crucial for the regulation of contraction and intracellular signaling, which are vital to heart function. Ca2+-activated signaling pathways must function against a background of large, rapid, and tightly regulated changes in intracellular free Ca2+ concentrations during each contraction and relaxation cycle (Fig. 3).

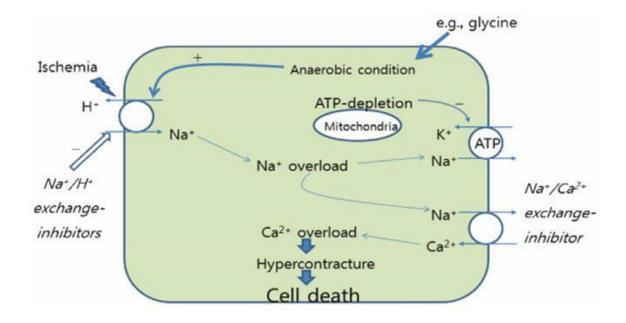


Fig. 3. Role of sodium- and calcium-overload in the pathogenesis of hyper contracture after cardiac ischemia/reperfusion

Ginsenoside Rb1 inhibits cardiac hypertrophy in a rat model [40]. Ginsenoside Rd reverses basilar hypertrophic remodeling in stroke-prone renovascular hypertensive rats as a new voltage-independent Ca2+ entry blocker [41] Also, the effect of sugar position in ginsenosides on inhibitory potency of Na+/K+-ATPase activity has been described [42] Another study reported that mutations in the Leu427, Asn428, and Leu431 residues attenuate ginsenoside-mediated L-type Ca2+ channel current inhibition The data indicate that ginsenosides inhibit Ca2+ entry, and so may ameliorate cardiac function. [43]

Ginseng and ginsenosides Prevent Alzheimer disease

Alzheimer is a neuro de-generative disorder affecting more than 26 million people worldwide. It is characterized by tau pathology and deposition of Ab in brain parenchyma in the form of plaques, accompanied by inflammation and neuronal damage .Platelets express APP, which contributes more than 90% of the circulating APP, are the main source of Ab deposition in cerebral blood vessels, and contribute to cerebral amyloid angiopathy in AD [44] Literature shows that Ab peptides stimulate platelet activation and enhance platelet aggregation and platelet thrombi in the vasculature, which further aggravate AD pathology after shrinkage or rupture of t The blood vessel [45] P.ginseng and ginsenosides are well known to inhibit platelet activation and they have also been documented to ameliorate Ad symptoms and improve cognitive functions [46] There is a great possibility that P.ginseng and ginsenosides may

ameliorate cognitive dysfunction and reduce Ab deposition in patients with AD by inhibiting platelet activation. Conversely, ginseng and ginsenosides will evoke endothelium-dependent vaso- relaxation, thereby reducing the chances of plaque rupture and vascular shrinkage. [47] 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 and Alzheimer disease.

Anti-inflammatory and anti-allergic effects of ginseng and ginsenosides.

More recently, the role of ginseng in modulation of inflammatory and allergic processes has been documented by some researchers. For example, Ginseng root saponins exerted an inhibitory effect on IL-1β and IL-6 gene expression in a chronic inflammation model of aged rats, ginsenosides Rb1 and Rg1 decreased TNF- α production by murine macrophages, pre treatment with ginsenoside Rg3 abrogated cyclooxygenase-2 expression in response to 12-O-tetra decanoyl phorbol-13acetate (TPA) in mouse skin, and ginsenosides Rb1 and Rc suppressed histamine and leukotriene release during the activation of guinea-pig lung mast cells, [48] the total saponins of Sanchi (Panax pseudo ginseng notoginseng) reduced the level of the intracellular Ca2+ concentration in neutrophils and ginseng had radioprotective effects against y-ray-induced DNA double strand breaks in cultured murine spleen lymphocytes. Furthermore, it was found that ginseng promoted the apoptosis of renal interstitial fibroblasts and thus affected renal interstitial fibrosis [49] Ginseng also has immunostimulant effects as it enhances interferon induction, phagocytosis, natural killer (NK) cells, and B and T cells in various animal species including mice and guinea pigs and also in humans, [50] the ginseng have ability to stimulate the immune system of dairy cows as it activated the innate immunity of cows and contributed to the cow's recovery from mastitis.[51]

Ginseng and ginsenosides inhibit platelet aggregation.

The Korean Red Ginseng shows an important effect on arterial thrombosis in vivo, which might be due to inhibition of platelet aggregation rather than anticoagulation, and this suggests that red ginseng treatment can be beneficial for individuals with cardiovascular impairment, [52] Another study reported that di hydro ginsenoside Rg3 powerfully inhibited platelet aggregation via downstream signaling such as cyclic adenosine-3', 5'-monophosphate (AMP) and extracellular signal-regulated kinase 2 [53] P. ginseng significantly decreased lipopolysaccharide-mediated microcirculatory troubles by preventing the adherence of leukocytes to the vascular wall, the degranulation of mast cell, and the release of various cytokines [54]. Also, ginsenosides Rg6, Rk3, Rh4, Rs3, Rs4, Rs5, and F4 extracted from processed ginseng were evaluated for platelet aggregation induced by adenosine diphosphate, collagen, and arachidonic acid. The results showed that ginsenosides Rs3, Rs4, and Rs5 had weak effects on aggregation induced by the three stimulators. Coadministration of Korean Red Ginseng and warfarin showed some synergistic interactions in patients with cardiac valve replacement [55] In ischemia and reperfusion injury of isolated rat hearts, coronary perfusion flow can be increased by total ginsenosides, indicating the protection of heart tissues by coronary artery dilation from I/R injury. This effective function of total ginsenosides is related to the activation of PI3K/Akt-eNOS pathway and NO formation, [56] Based on these results, studies suggest that in vivo ginseng or ginsenosides have an important antithrombotic effect that would be beneficial for individuals with thrombotic problems and cardiovascular diseases .

ANTI-CARCINOGENIC EFFECT OF GINSENG

Although some of ginseng's activities against cancer have already been reviewed elsewhere, in this section we try to focus on the most common and recent findings related to the anti-cancer effect of ginseng. Researchers have reported that chronic intake of Panax ginseng decreased the incidence of cancers such as lung, gastric, liver and colorectal tumors [57] Ginsenoside Rh2 has been shown to suppress proliferation in a number of human cancer cells including breast, prostate, hepatic and intestinal cancer, but also in animal cell lines [58] Ginsenosides Rb1, Rb2 and Rc inhibited tumor angiogenesis and metastasis while ginsenoside Rh1 inhibited proliferation of the NIH 3T3 mouse fibroblast cell line [59] the ginsenoside Rg3 treatment caused marked suppression of TPA-induced cyclooxygenase-2 (COX2) expression in mouse skin and in human breast epithelial cells (MCF-10A). Also, the same suppressive effect on NF-κB in mouse skin and extracellular regulated protein kinases (ERK) activation in TPA stimulated MCF-10A cells. [60] the topical application of ginseng extract prior to each topical dose of the tumor promoter TPA markedly lowered the papilloma formation in mouse skin and caused substantial reduction in epidermal ornithine decarboxylase (ODC) activity and suppressed the expression of its mRNA. All of the above mentioned enzymes and factors are, in part, involved in tumorogenesis. COX-2 was upregulated in transformed cells and in various forms of cancer. Its overexpression inhibited apoptosis and increased the invasiveness of tumor cells [61] ODC is a rate-limiting enzyme in the biosynthesis of polyamines that play a pivotal role in cell proliferation and tumor promotion [62] The mitogen activated protein kinase (MAPK) cascade is responsible, in part, for upregulation of COX-2 as specific inhibitors of the corresponding MAPK abolish the induction of COX-2 and result in production of prostaglandin E2 [63] NF- κ B is a ubiquitous eukaryotic transcription factor implicated in cellular proliferation and malignant transformation. Its activation by oncogenic Ras is an essential early event prior to malignant transformation [64].

Antiplatelet effects of ginseng

Recently, the study summarized and reported the Antiplatelet and antithrombotic effects of P. ginseng and several ginsenosides [65] There are many similarities and differences among the pharmacological and therapeutic effects of P. ginseng, and its ginsenosides,

on vascular endothelial cells and platelets which may indicate its potential adaptogenic properties (Table 1). [66] An interesting and classical example is that P. ginseng or ginsenosides cause vasorelaxation by NO production through stimulation of the eNOS-PI3K/Akt pathway in vascular endothelial cells but produce Antiplatelet and antithrombotic effects by

inhibiting the PI3K/Akt pathway [67] 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.

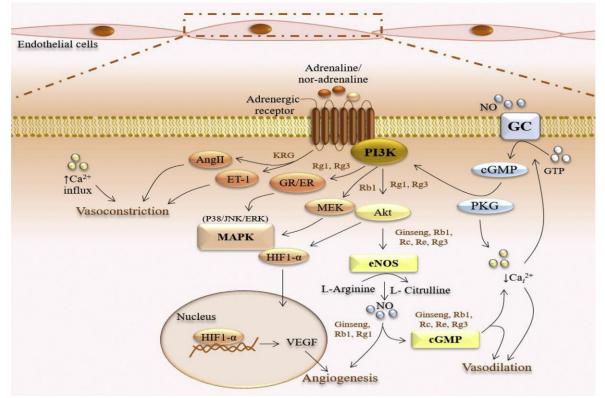


Fig.4. Effect of P. ginseng and ginsenosides on vascular endothelial cells.

Ginseng/ginsenoside	Platelets	Endothelial cells	Ginseng/ginsenoside

Rg3, 2HRg3, Rpl, Rp3, Ro,	cAMP	cGMP	Rb1, Rc, Re
TS, NSF			
Rg1, Rg2, Rg3, 2HRg3,	Inhibit Pl3K/Akt	Activate PI3K/Akt	Rb1, Rc, Re
Rp1, Rp3, Rp4, gintonin			
Rg3, 2HRg3, Ro, Rpl, Rp3,	Inhibit MAPK	Activate MAPK	Rb1, Rc, Re
Rp4, TS, NSF, gintonin	NO in stimulated	NO via eNOS	Ginseng, Rb1, Rc, Re, Rg3
	platelets		
Rg3, 2HRg3, Rp1, Rp3,	VASP phosphorylation	Vasorelaxation	Ginseng, Rbl, Rc, Re, Rg3
Ro, TS, NSF			
Rbl, Rc, Re	Antihypertension	Antihypertension	Ginseng, Rbl, Rc, Re, Rg3
NDI, NC, NC	Antinypertension	Antinypertension	Ginseng, Kbi, Kc, Ke, Kg5
Ginseng, Rg3			
	Improved blood flow	Improved blood	Ginseng, Rb1, Rc, Re, Rg3, Rf1
		flow	

Table 1 .Comparative effects of P. ginseng and ginsenosides on platelet and endothelial cells

Other pharmacological effects of ginseng

Ginseng and its constituents, ginsenosides, have a number of other pharmacological actions including antipyretic activity, increase of gastro-intestinal tract motility, and acceleration of glycolysis and cholesterol synthesis as well as increased synthesis of serum proteins [68] Another important biological effect reported for Panax ginseng or its saponins is hypoglycemic and anti hyperglycemic activity and ginsenoside Rg1 increased the number of insulin receptors and panaxan B, the main constituent of Panax ginseng for hypoglycemic activity, increased the plasma insulin level and enhanced insulin sensitivity [69] Ginseng also shows anti-stress activities against physical, chemical, and biological stressful circumstances. For instance, it was shown that treatment with root saponins partially prevented the rectal temperature decline in normal rats exposed to cold stress [70] extracts of Panax ginseng had radioprotective effects or prolonged the survival time of irradiated mice and accelerated the hematological recovery of mice after xray irradiation as well as reduced DNA damage in normal cells [71] ginseng can moderate chemical stress as it decreased damage to rat liver and inhibited the elevation of serum glutamic pyruvic transaminase in carbon tetrachloride or thioacetamide-intoxicated mice and also Panax ginseng saponins-treated mice were found to be more resistant to infections by Staphylococcus aureus, Escherichia coli, and Salmonella typhi [72] the aqueous extract of ginseng radix produced

beneficial effects against gastritis and ginsenoside Rb1 had an anti-ulcer effect through increasing mucus secretion [73]

Subject	Ginseng effects	Possible action
Whole body	General tonic and adaptogen.	- Resistance against adverse
		conditions (physical,
		chemical, and biological
		factors,
		Restores body's homeostasis,
		Anti-aging effects.
Central Nervous system	Neuroprotection either in	Potentiates nerve growth
	vivo or in vitro	factor,
		Anti-oxidative and anti-
		apoptotic mechanisms,
		Reduces lipid peroxidation,
		Inhibits excitotoxicity and
		Ca2+ over-influx into
		neurons,
		Maintains cellular ATP levels,
		Preserves structural integrity
		of neurons.
Cardiovascular system.	Antihypertensive	
		Relaxes vascular smooth
		muscle cells through NO and
		Ca2+ mediated mechanisms,
		Inhibits production of
		endothelin which plays a role
		in blood vessel constriction,
		Prevents platelet
		aggregation,
		Suppresses thrombin
		formation.
Inflammation and allergy.	Anti-inflammatory and anti-	
	allergic effects.	
		Inhibits cytokine production
		such as IL-1 β , IL-6, and TNF-
		α,

		Abrogates cyclooxygenase-2 gene expression, Suppresses histamine and leukotrienes release from mast cells, Stabilizes inflammatory cells
Immune system.	Immunostimulant.	such as neutrophils and lymphocytes, Antifibroblastic activity.
Carcinogenesis.	Anti-carcinogenic effect.	Enhances interferon induction, phagocytosis, natural killer cells, and B and T cells.
Aphrodisiac effect.	Enhancement of male copulatory behavior.	Suppresses malignant transformation, Inhibits proliferation of tumor cells, Inhibits tumor invasiveness, metastasis, and angiogenesis.
		Relaxes corpus cavernosum smooth muscles via NO mediated processes, increases serum testosterone levels and reduces plasma levels of prolactin hormone, Direct effects on anterior pituitary and hypothalamic dopaminergic mechanisms
Hyperglycemia.	Antihyperglycemic activity	

	Increases plasma insulin
	levels, number of insulin
	receptors and insulin
	sensitivity.

Table 2. Important ginseng effects and its possible actions on different body systems

Clinical aspects of ginseng

Based on the medical history and experimentally promising results of ginseng, ginseng and its components have recently been introduced into the clinic. It has been used as a curative substance to enhance the general performance, immunity, and mood of patients, particularly post-operatively. The relevant clinical trials regarding the effect of ginseng on cardiovascular diseases are managing hypertension and improving cardiovascular function and It could also improve cardiac function in patients suffering from congestive heart failure [74] the levels of serum cardiac troponin T (c TnT), a specific marker reflecting myocardial injury, was effectively reduced after treatment with the ginseng-containing Shenmai injection in congestive heart failure patients [75] Some current studies have shown the role of ginseng in reducing the side effects of either chemo- or radiotherapy in cancer patients. For example, ginseng could inhibit the recurrence of American Joint Committee on Cancer (AJCC) stage III gastric tumor and showed immune modulatory activities during post-operative chemotherapy. Moreover, red ginseng also increased the overall survival of patients during post-operative chemotherapy in comparison with the matched control [76] the ginseng-containing Shen-Qi injection could reduce the toxic effects produced by chemical agents in patients suffering from digestive tract tumors. This effect seemed to be mediated by increasing the cellular immunologic function as assessed by phagocytic index, percentage of phagocytes, T lymphocyte transformation rate, and esterase staining [77] Regarding the toxic effect of radiotherapy, it has been reported that ginseng polysaccharides have certain effects on improvement of immune function in nasopharyngeal carcinoma patients during radiotherapy treatment [78] the activity of natural killer cells and lymphocyte-activated killer cells was significantly increased in the peripheral blood of patients undergoing radiotherapy with simultaneous administration of ginseng polysaccharides compared to patients not receiving ginseng polysaccharides. Moreover, one of the future promising effects of ginseng is treatment of the irritable bowel syndrome (IBS) since it was shown that protopanaxatriol (PT) ginsenosides attenuated the experimentally-induced visceral hypersensitivity [79] the ginseng has been reported to possess positive effects against herpes simplex type-II infections and diabetes mellitus, common cold symptom complex, ethanolinduced gastric lesion, and aspirin-induced gastric ulcers [80]

Summary

The present review summarizes information regarding the efficacy of ginseng and ginsenosides on primary cardiovascular risk factors such as dysfunction of ion regulation, signal transduction problems, oxidative stress, platelet aggregation, hypertension, hyperlipidemia, and cardiac ischemia. Ginseng and ginsenosides play a primary role in preventing cardiovascular disease. As shown previously, ginseng and ginsenosides showed significant effects on cardiovascular disease through the inhibition of ROS formation, stimulation of NO generation, enhancement of vasomotor tone, improvement in blood circulation, and amelioration of lipid profile. However, the exact action mechanism of ginseng and ginsenosides remain unidentified. In the future, the specific mechanism of ginseng and ginsenoside against cardiovascular impairment must be studied. The common use of ginseng and ginsenosides as natural medicine requires verification to verify its efficacy and safety.

Conflicts of interest

The authors have no conflict of interest

REFRENCES

1. Jong-Hoon Kim Department of physiology, College of veterinary medicine, chonbuk national university, iksan Republic of Korea Journal of Ginseng Research J Ginseng Res 42 (2018) 264-269

2. World Health Organization. World Health Organization; Geneva: 1999. WHO monographs on selected medicinal plants. [Google Scholar]

3. Nocerino E, Amato M, Izzo AA. The aphrodisiac and adaptogenic properties of ginseng. Fitoterapia. 2000;71:1–5.

4. Wen TC, Yoshimura H, Matsuda S, Lim JH, Sakanaka M. Ginseng root prevents learning disability and neuronal loss in gerbils with 5-minute forebrain ischaemia. Acta Neuropathol. 1996;91:15–22.

5. Smolinski AT, Pestka JJ. Modulation of lipopolysacchrideinduced proinflammatory cytokine production in vitro and in vivo by the herbal constituents apigenin (chamomile), ginsenoside Rb1 (ginseng) and parthenolide. Food Chem Toxicol. 2003;41:1381–1390

6. Buettner C., Yeh G.Y., Phillips R.S., Mittleman M.A., Kaptchuk T.J. Systematic review of the effects of ginseng on cardiovascular risk factors. Ann Pharmac other. 2006;40:83–95. [PubMed] [Google Scholar]

7. Cheng Y., Shen L.H., Zhang J.T. Anti-amnestic and anti-aging effects of ginsenoside Rg1 and Rb1 and its mechanism of action. Acta Pharmacol Sin. 2005;26:143–149. [PubMed] [Google Scholar]

8. Liberti LE, Der Mardersian A. Evaluation of commercial ginseng products. J Pharm Sci. 1978;10:1487–1489.

9. Lim K.H., Ko D., Kim J.H. Cardioprotective potential of Korean Red Ginseng extract on isoproterenol-induced cardiac injury in rats. J Ginseng Res. 2013;37:273–282. [PMC free article] [PubMed] [Google Scholar]

10. Toth P.P. Making a case for quantitative assessment of cardiovascular risk. J Clin Lipidol. 2007;1:234–241. [PubMed] [Google Scholar]

11. Libby P. Act local, act global: inflammation and the multiplicity of "vulnerable" coronary plaques. J Am Coll Cardiol. 2005;45:1600–1602. [PubMed] [Google Scholar]

12. Davies M.J., Gordon J.L., Gearing A.J., Pigott R., Woolf N., Katz D., Kyriakopoulos A. The expression of the adhesion molecules ICAM-1, VCAM-1, PECAM, and Eselectin in human atherosclerosis. J Pathol. 1993;171:223–229. [PubMed] [Google Scholar]

13. Nah S.Y., Kim D.H., Rhim H. Ginsenosides: are any of them candidates for drugs acting on the central nervous system? CNS Drug Rev. 2007;13:381–404. [PMC free article] [PubMed] [Google Scholar]

14 . Brekhman I, Dardymov I. New substances of plant origin which increase non specific resistance. Ann Rev Pharmacol. 1969;9: 419–430

15. O'Hara M, Kiefer D, Farrell K, Kemper K. A review of 12 commonly used medicinal herbs. Arch Fam Med. 1998;7:523–536

16. Qi L.W., Wang C.Z., Yuan C.S. Isolation and analysis of ginseng: advances and challenges. Nat Prod Rep. 2011;28:467–495. [PMC free article] [PubMed] [Google Scholar]

17. Qi L.W., Wang C.Z., Yuan C.S. Isolation and analysis of ginseng: advances and challenges. Nat Prod Rep. 2011;28:467–495. [PMC free article] [PubMed]

18. Leung K.S., Chan K., Bensoussan A., Munroe M.J. Application of atmospheric pressure chemical ionisation mass spectrometry in the identification and differentiation of Panax species. Phytochem Anal. 2007;18:146–150

19. Kim S.I., Park J.H., Ryu J.H., Park J.D., Lee Y.H., Park J.H., Kim T.H., Baek N.I. Ginsenoside Rg5, a genuine dammarane glycoside from Korean red ginseng. Arch Pharm Res. 1996;19:551–553

20. . Kim W.Y., Kim J.M., Han S.B., Lee S.K., Kim N.D., Park M.K., Kim C.K., Park J.H. Steaming of ginseng at high temperature enhances biological activity. J Nat Prod. 2000;63:1702–1704.

21. Yamaguchi Y, Higashi M, Kobayashi H. Effects of ginsenosides on impaired performance caused by scopolamine in rats. Eur J Pharmacol. 1996;312:149–151.

22. Kurimoto H, Nishijo H, Uwano T, Yamaguchi H, Zhong YM, Kawanishi K, et al. Effects of nonsaponin fraction of red ginseng on learning deficits in aged rats. Physiol Behav. 2004;82:345–355.

23. Shen L, Zhang J. Ginsenoside Rg1 increases ischemia-induced cell proliferation and survival in the dentate gyrus of adult gerbils. Neurosci Lett. 2003;344:1–4.

24. Bolli R. Superoxide dismutase 10 years later: a drug in search of a use. J Am Coll Cardiol. 1991;18:231–233..

25. Li J., Ichikawa T., Jin Y., Hofseth L.J., Nagarkatti P., Nagarkatti M., Windust A., Cui T. An essential role of Nrf2 in American ginseng-mediated anti-oxidative actions in cardiomyocytes. J Ethnopharmacol. 2010;130:222–230.

26. Zhou W., Chai H., Lin P.H., Lumsden A.B., Yao Q., Chen C. Ginsenoside Rb1 blocks homocysteine-induced endothelial dysfunction in porcine coronary arteries. J Vasc Surg. 2005;41:861–868

27. Deng H.L., Zhang J.T. Anti-lipid peroxilative effect of ginsenoside Rb1 and Rg1. Chin Med J (Engl) 1991;104:395–398.

28. He F., Guo R., Wu S.L., Sun M., Li M. Protective effects of ginsenoside Rb1 on human umbilical vein endothelial cells in vitro. J Cardiovasc Pharmacol. 2007;50:314–320

29. Xie J.T., Shao Z.H., Vanden Hoek T.L., Chang W.T., Li J., Mehendale S., Wang C.Z., Hsu C.W., Becker L.B., Yin J.J. Antioxidant effects of ginsenoside Re in cardiomyocytes. Eur J Pharmacol. 2006;532:201–207

30. Kritharides L, Brown A, Brieger D, Ridell T, Zeitz C, Jeremy R, Tonkin A, Walsh W, White H. Overview and determinants of cardiovascular disease in indigenous populations. Heart Lung Circ 2010;19:337-343.

31. Pratt C. Alternative prevention and treatment of cardiovascular disease, part 2. Prim Care 2010;37:339-366.

32. Ulrich S, Hingorani AD, Martin J, Vallance P. Lifetime risk of developing coronary heart disease. Lancet 1999;353:925 33. Davies MJ, Gordon JL, Gearing AJ, Pigott R, Woolf N, Katz D, Kyriakopoulos A. The expression of the adhesion molecules ICAM-1, VCAM-1, PECAM, and E-selectin in human atherosclerosis. J Pathol 1993;171:223-229.

34. Shibata S, Fujita M, Itokawa H, Tanaka O, Ishii T. Studies on the constituents of Japanese and Chinese crude drugs. XI. Panaxadiol, a sapogenin of ginseng roots. Chem Pharm Bull (Tokyo) 1963;11:759-761.

35. Deng J., Wang Y.W., Chen W.M., Wu Q., Huang X.N. Role of nitric oxide in ginsenoside Rg(1)induced protection against left ventricular hypertrophy produced by abdominal aorta coarctation in rats. Biol Pharm Bull. 2010;33:631–635.

36. 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;31:1530–1535.

37. Zhu D., Wu L., Li C.R., Wang X.W., Ma Y.J., Zhong Z.Y., Zhao H.B., Cui J., Xun S.F., Huang X.L. Ginsenoside Rg1 protects rat cardiomyocyte from hypoxia/reoxygenation oxidative injury via antioxidant and intracellular calcium homeostasis. J Cell Biochem. 2009;108:117–124.

38. Guo J., Gan X.T., Haist J.V., Rajapurohitam V., Zeidan A., Faruq N.S., Karmazyn M. Ginseng inhibits cardiomyocyte hypertrophy and heart failure via NHE-1 inhibition and attenuation of calcineurin activation. Circ Heart Fail. 2011;4:79–88.

39. Dong-Ha Lee D.H., Cho H.J., Kim H.H., Rhee M.H., Ryu J.H., Park J.H. Inhibitory effects of total saponin from Korean red ginseng via vasodilator-stimulated phosphoprotein-Ser157 phosphorylation on thrombin-induced platelet aggregation. J Ginseng Res. 2013;37:176–186.

40. Jiang QS, Huang XN, Dai ZK, Yang GZ, Zhou QX, Shi JS, Wu Q. Inhibitory effect of ginsenoside Rb1 on cardiac hypertrophy induced by monocrotaline in rat. J Ethnopharmacol 2007;111:567-572.

41 Haq, I., Muhammad, A., Fazli Zahir, M. K., Anwar, F., Akhtar, M. S., & Ullah, F. (2020). Serological and Epidemiology study of Helicobacter pylori infection among Dyspeptic patients in District Peshawar Pakistan. Adv. Biores, 11(3), 81-85.

42. Qamar, Z., Anwar, F., Ahmad, R., Haq, I., Khan, A. M. K., Hussain, R., ... & Khan, J. (2021). Prevalence of Hepatitis C virus and determination of its genotypes in subjects of Tehsil Daggar District Buner, KP, Pakistan. Clinical Epidemiology and Global Health, 12, 100809.

43. Choi SH, Lee JH, Pyo MK, Lee BH, Shin TJ, Hwang SH, Kim BR, Lee SM, Oh JW, Kim HC et al. Mutations Leu427, Asn428, and Leu431 residues within transmembrane domain-I-segment 6

attenuate ginsenoside-mediated L-type Ca(2+) channel current inhibitions. Biol Pharm Bull 2009;32:1224-1230.

44. Vuksan V., Stavro M., Woo M., Leiter L.A., Sung M.K., Sievenpiper J.L. Proceedings of the 9th International Ginseng symposium. Geumsan: Korean Society of Ginseng. 2006. Korean red ginseng (Panax ginseng) can lower blood pressure in individuals with hypertension: a randomized controlled trial; pp. 35–36.

45. Baek E.B., Yoo H.Y., Park S.J., Chung Y.S., Hong E.K., Kim S.J. Inhibition of arterial myogenic responses by a mixed aqueous extract of Salvia miltiorrhiza and Panax notoginseng (PASEL) showing antihypertensive effects. Korean J Physiol Pharmacol. 2009;13:287–293.

46. 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;31:1530–1535

47. Wu Y., Xia Z.Y., Dou J., Zhang L., Xu J.J., Zhao B., Lei S., Liu H.M. Protective effect of ginsenoside Rb1 against myocardial ischemia/reperfusion injury in streptozotocin-induced diabetic rats. Mol Biol Rep. 2011;38:4327–4335.

48. Yu SC, Li XY. Effect of ginsenoside on IL-1 beta and IL-6 mRNA expression in hippocampal neurons in chronic inflammation model of aged rats. Acta Pharmacol Sin. 2000;21:915–918.

49. Zhang GQ, Ye RG, Kong QY, Yang NS, Zhang JL, Guan WM, et al. Panax notoginseng saponins induced of human renal interstitial fibroblast and its mechanisms. Chin J Nephrology. 1998;14:93–95.

50. Matsuda H, Kubo M, Tani T, Kitagawa I, Mizuno M. [Pharmacological study of Panax ginseng C. A. Meyer (IX). Protective effect of red ginseng on interferon (2) on phagocytic activity of mouse reticuloendothelial cells system]. Shoyakugaku Zasshi. 1987;41:135–141. (text in Japanese with English abstract

51. Hu S, Concha C, Johannisson A, Meglia G, Waller KP. Effect of subcutaneous injection of ginseng on cows with subclinical Staphylococcus aureus mastitis. J Vet Med B Infect Dis Vet Public Health. 2001;48:519–528.

52. Asif, A., Asghar, M., Khan, H. U., Haq, I., Shuaib, S. L., Khalid, F., ... & Rehman, N. (2021). Antibiotic susceptibility pattern of clinical isolates of methicillin resistant staphylococcus aureus in Peshawar, Pakistan. Annals of the Romanian Society for Cell Biology, 25(6), 20116-20131. 53. Yi X.Q., Li T., Wang J.R., Wong V.K., Luo P., Wong I.Y., Jiang Z.H., Liu L., Zhou H. Total ginsenosides increase coronary perfusion flow in isolated rat hearts through activation of PI3K/Akt-eNOS signaling. Phytomedicine. 2010;17:1006–1015.

54 Anwar, F., Khan, M., Salman, M., Ahmad, S., Ullah, F., Khan, J., ... & Abbas, M. (2021). Seroprevalence of hepatitis B virus in human population of district Buner Khyber Pakhtunkhwa Pakistan. Clinical Epidemiology and Global Health, 10, 100688

55. Jan, Z., Ahmad, S. U., Amara Qadus, Y. A., Sajjad, W., Rais, F., Tanveer, S., ... & Haq, I. (2021). 19. Insilico structural and functional assessment of hypothetical protein L345_13461 from Ophiophagus hannah. Pure and Applied Biology (PAB), 10(4), 1109-1118.

56. Rehman, A., Haq, I., Asghar, M., Afridi, G. Z., & Faisal, S. (2020). Sero-epidemiological Identification of Dengue Virus in Individuals at District Shangla, Khyber Pakhtunkhwa. Pakistan. J Biomedical Sci, 9(3), 10.

57. Yun TK. Experimental and epidemiologic evidence of cancer preventive effects of Panax ginseng C.A. Meyer. Nutr Rev 1996;54:71-81.

58. Lee YN, Lee HY, Chung HY, Kim SI, Lee SK, Park BC, Kim KW. In vitro induction of differentiation by ginsenoides in F9 teratocarcinoma cells. Eur J Cancer 1996;32:1420-1428

59. Byun BH, Shin I, Yoon YS, Kim SI, Joe CO. Modulation of protein kinase C activity in NIH 3T3 cells by plant glycosides from Panax ginseng. Planta Med 1997;63:389-392.

60. Surh YJ, Na HK, Lee JY, Keum YS. Molecular mechanisms underlying anti-tumor promoting activities of heat-processed Panax ginseng C.A. Meyer. J Korean Med Sci 2001;16:38-41.

61. Subbaramaiah K, Telang N, Ramonetti JT, Araki R, DeVito B, Weksler BB, Dannenberg AJ. Transcription of cyclooxygenase-2 is enhanced in transformed mammary epithelial cells. Cancer Res 1996;6:4424-4429.

62 ul Haq, I., Khan, M., Rehman, Z., Anwar, F., Ullah, H., & Ullah, N. (2018). HBV prevalence in the volunteer blood donors in Peshawar, Khyber Pakhtunkhwa Pakistan. Int J Biosci, 13(5), 50-54

63. Bashir, Z., Ahmad, S. U., Kiani, B. H., Jan, Z., Khan, N., Khan, U., ... & Mahmood, T. (2021).Immuno informatics approaches to explore B and T cell epitope-based vaccine designing for SARS-CoV-2 Virus. Pak. J. Pharm. Sci, 34(1), 345-352

64. Mayo MW, Wang CY, Congswell PC, Rogers-Graham KS, Lowe SW, Der CJ, et al. Requirement of NF-κB activation to suppress p53-independent apoptosis induced by oncogenic Ras. Science. 1997;278:1812–1915.

65. Jeong D, Irfan M, Kim S-D, Kim S, Oh J-H, Park C-K, et al. Ginsenoside Rg3enriched red ginseng extract inhibits platelet activation and in vivo thrombus formation. J Ginseng Res 2017;41(4):548e55.

66. Khalid, F. (2021). Comparative Diagnostic Analysis and Biochemical Profile in Patients with Covid-19, Dengue and Acute Febrile Illness: Suggestions for Patient Controlling. Annals of the Romanian Society for Cell Biology, 25(7), 1733-1744.

67. 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):264e9.

68. Long MZ, Wang DB, Yang JM. [Clinical study on effect of Shenmai injection in treating congestive heart failure]. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2003;23:808–810. (text in Chinese with English abstract)

69. 6 Long MZ, Wang DB, Yang JM. [Clinical study on effect of Shenmai injection in treating congestive heart failure]. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2003;23:808–810. (text in Chinese with English abstract)

70. Suh SO, Kroh M, Kim NR, Joh YG, Cho MY. Effects of red ginseng upon postoperative immunity and survival in patients with stage III gastric cancer. Am J Chin Med. 2002;30:483–494.

71. Li NQ. [Clinical and experimental study on shen-qi injection with chemotherapy in the treatment of malignant tumor of digestive tract]. Zhongguo Zhong Xi Yi Jie He Za Zhi. 1992;12:588–592. (text in Chinese with English abstract)

72. Xie FY, Zeng ZF, Huang HY. [Clinical observation on nasopharyngeal carcinoma treated with combined therapy of radiotherapy and ginseng polysaccharide injection]. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2001;21:332–334. (text in Chinese with English abstract)

73. Kim JH, Lee JH, Jeong SM, Lee BH, Yoon IS, Lee JH, et al. Effect of ginseng saponins on a rat visceral hypersensitivity model. Biol Pharm Bull. 2005;28:2120–2124.

74. Kaneko H, Nakanishi K. Proof of the mysterious efficacy of ginseng: basic and clinical trials: clinical effects of medical ginseng, korean red ginseng: specifically, its anti-stress action for prevention of disease. J Pharmacol Sci. 2004;95:158–162.

75. Rudakewich M, Ba F, Benishin CG. Neurotrophic and neuroprotective actions of ginsenosides Rb1 and Rg1. Planta Med. 2001;67:533–537

76. Tode T, Kikuchi Y, Hirata J, Kita T, Nakata H, Nagata I. Effect of Korean red ginseng on psychological functions in patients with severe climacteric syndromes. Int J Gynaecol Obstet. 1999;67:169–174.

77. Wang LC, Lee TF. Effect of ginseng saponins on cold tolerance in young and elderly rats. Planta Med. 2000;66:144–147.

78. Kim C, Choi JE. Effect of radioprotective ginseng protein on UV-induced sister chromatid exchanges. Arch Pharm Res. 1988;11:93–98

79. Wang BX, Cui JC, Liu AJ. The effect of ginseng on immune responses. In: Chang HM, Yeung HW, Tso W-W, Koo A, editors. Advance in Chinese medicinal materials research. Singapore/Philadelphia: World Scientific Publishing; 1985. p. 62–64.

80. Jeong CS, Hyun JE, Kim YS. Ginsenoside Rb1: the anti-ulcer constituent from the head of Panax ginseng. Arch Pharm Res. 2003;26:906–911