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Critical Review

Use of Ginseng in Medicine With Emphasis on Neurodegenerative Disorders

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Abstract. Ginseng, the root of *Panax* species, is a well-known herbal medicine. It has been used as a traditional medicine in China, Korea, and Japan for thousands of years and is now a popular and worldwide used natural medicine. The active ingredients of ginseng are ginsenosides which are also called ginseng saponins. Recently, there is increasing evidence in the literature on the pharmacological and physiological actions of ginseng. However, ginseng has been used primarily as a tonic to invigorate week bodies and help the restoration of homeostasis. Current in vivo and in vitro studies have shown its beneficial effects in a wide range of pathological conditions such as cardiovascular diseases, cancer, immune deficiency, and hepatotoxicity. Moreover, recent research has suggested that some of ginseng's active ingredients also exert beneficial effects on aging, central nervous system (CNS) disorders, and neurodegenerative diseases. In general, antioxidant, anti-inflammatory, anti-apoptotic, and immune-stimulatory activities are mostly underlying the possible ginseng-mediated protective mechanisms. Next to animal studies, data from neural cell cultures contribute to the understanding of these mechanisms that involve decreasing nitric oxide (NO), scavenging of free radicals, and counteracting excitotoxicity. In this review, we focus on recently reported medicinal effects of ginseng and summarize the current knowledge of its effects on CNS disorders and neurodegenerative diseases.

Keywords: ginseng, ginsenoside, central nervous system, herbal medicine, Chinese herb

Introduction

Ginseng refers to the root of several species in the plant genus *Panax* (C.A. MEYER Araliaceae). Among them, *Panax ginseng* is the most widely used ginseng and is indigenous to the Far East countries (most notably China and Korea). *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 (1). In China, ginseng roots are harvested when the plant is 3 – 6-year-old, and then the roots are submitted to air drying (white ginseng) or are steamed (red ginseng). Interestingly, after these two ways of treatment, the roots differ in their content of saponins (1) and this may be the reason for the variable actions of different ginseng products. Other species of the genus *Panax* include *Panax quinquefolius* (found in southern Canada and in the United States), *Panax japonicus* (grown in Japan), and less frequently, *Panax notoginseng* (grown in China), *Panax pseudoginseng* (grown in Nepal and eastern Himalayas), and *Panax vietnamensis* (grown in Vietnam) (2).

Ginseng is a widespread herbal medicine (3) and it has served as an important component of many Chinese

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prescriptions since thousands of years (4, 5). 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 (6). Moreover, it is estimated that more than six million Americans are regularly consuming ginseng products (7). Ginseng is believed not only to engender physical benefits, but also to have positive effects on cognitive performance and well-being.

Ginsenosides or ginseng saponins are the principle active ingredients in ginseng and more than thirty different ginsenosides have been identified (8, 9). Ginsenosides are unique to *Panax* species, many of which exist in minute amounts and are believed to be responsible for most of ginseng's actions (10 – 13). Additionally, ginsenosides operate by many mechanisms and it was suggested that each ginsenoside may have its own specific tissue-dependent effects (14). The basic structure of ginsenosides is similar. They consist of a gonane steroid nucleus with 17 carbon atoms arranged in four rings. The characteristic biological responses for each ginsenoside are attributed to the differences in the type, position, and number of sugar moieties attached by the glycosidic bond at C-3 and C-6 (15). Based on their structural differences, they can be classified into three categories: the panaxadiol group (e.g., Rb1, Rb2, Rb3, Rc, Rd, Rg3, Rh2, Rs1), the panaxatriol group (e.g., Re, Rf, Rg1, Rg2, Rh1), and the oleanolic acid group (e.g., Ro) (5, 16). 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 (17, 18).

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 central nervous system (CNS) disorders.

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 (1, 19). 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 (12, 20).

Neuropharmacology of ginseng

Ginseng rescues neuronal cells either in vivo or in vitro

Recently, it has been shown that ginseng and its components, ginsenosides, have a wide range of actions in the CNS (21). These effects include increased cell survival, extension of neurite growth, and rescuing of neurons from death in consequence of different insults either in vivo or in vitro. Sugaya et al. (22), Himi et al. (4), and Mizumaki et al. (23) reported that ginseng roots appeared to facilitate survival and neurite extension of cultured cortical neurons, and Kim et al. (24) showed that ginsenosides Rb1 and Rg3 protected neurons from glutamate-induced neurotoxicity. Following forebrain ischemia in gerbils, Wen et al. (5) and Lim et al. (25) demonstrated that central infusion of ginsenoside Rb1 rescued the hippocampal CA1 neurons against lethal damage of cellular hypoxia. Using a spinal neuron model, ginsenosides Rb1 and Rg1 proved to be potentially effective therapeutic agents for spinal cord injuries as they protected spinal neurons from excitotoxicity induced by glutamate and kainic acid and oxidative stress induced by hydrogen peroxide (26).

Ginseng's role in Parkinson's disease models

A number of studies have recently described the beneficial effect of ginseng and its main components, ginsenosides, on some neurodegenerative disease models. Special interest has been paid on Parkinson's disease (PD) models either in vivo or in vitro. In an in vivo model, Van Kampen et al. (21) reported that prolonged oral administration of ginseng extract G115 significantly protected against neurotoxic effects of parkinsonism-inducing agents such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and its active metabolite 1-methyl-4-phenylpyridinium (MPP^+) in rodents. He found that ginseng-treated animals sustained less damage and TH^+ neuronal loss in substantia nigra pars compacta (SNpc) after MPP^+ exposure. Likewise, reduction of TH immunoreactivity in the striatum was effectively diminished as a result of ginseng treatment compared to MPP^+-exposed animals. Similarly, striatal dopamine transporter (DAT) was significantly preserved due to ginseng treatment. In vitro studies showed that ginseng saponins enhanced neurite growth of dopaminergic SK-N-SH neuroblastoma cells (27). Recently, we demonstrated that ginsenosides Rb1 and Rg1 increased the survival of primary cultured dopaminergic cells and promoted their neuritic growth after exposure to either MPP^+ or glutamate (28, 29). Interestingly, Tanner and

Ben-Schlomo (30) speculated that geographic variations in PD prevalence might reflect ginseng consumption as in North America, PD occurs in approximately 200 cases per 100,000 persons compared to only 44 cases per 100,000 in China. On the other hand, this variation in PD prevalence in different populations may strengthen the familial theory of PD rather than consumption of ginseng.

Although the processes and mechanisms underlying the neuroprotective effects of ginseng upon dopaminergic neurons remain to be elucidated, several reports demonstrate the inhibitory role of ginseng on MPP^+ uptake in dopaminergic neurons, the suppression of oxidative stress induced by autooxidation of dopamine, the attenuation of MPP^+-induced apoptosis, and the potentiation of nerve growth factor (NGF). It has been shown that certain ginsenosides inhibit dopamine uptake into rat synaptosomes (31) and consequently ginseng could potentially provide protection against MPP^+ through blockade of its uptake by dopaminergic neurons (21). Ginsenoside Rg1 was shown to interrupt dopamine-induced elevation of reactive oxygen species (ROS) or NO generation in pheochromocytoma cells (PC12) (32). Kim et al. (33) and Chen et al. (34) reported that Ginseng radix attenuated MPP^+-induced apoptosis as it decreased the intensity of MPP^+-induced DNA laddering in PC12 cells and ginsenoside Rg1 had protective effects against MPTP-induced apoptosis in the mouse substantia nigra. These anti-apoptotic effects of ginseng may be attributed to enhanced expression of Bcl-2 and Bcl-xl, reduced expression of bax and nitric oxide synthase (NOS), and inhibited activation of caspase-3. Ginseng may also reverse the neurotoxic effects of MPP^+ through elevation of NGF mRNA expression (21). In accordance, Salim et al. (35) showed that ginsenosides Rb1 and Rg1 elevate NGF mRNA expression in rat brain and Rudakewich et al. (36) concluded that both ginsenosides potentiate NGF-induced neurite outgrowth in cell culture. Furthermore, it has been reported that ginsenosides Rb1, Rg1, Rc, and Re inhibited tyrosine hydroxylase activity and exhibited anti-dopaminergic action since they reduced the availability of dopamine at presynaptic dopamine receptors (37).

There are few reports concerning the effect of ginseng on other neurodegenerative diseases. For example, Jiang et al. (38) and Lee et al. (39) reported that ginseng and its components prevent neuronal loss in amyotrophic lateral sclerosis models and Ginseng radix has also been used for treatment of Alzheimer's disease.

General mechanisms and processes underlying neuropharmacology of ginseng

In addition to the mechanisms involved in neuroprotection of dopaminergic neurons, there exist additional data demonstrating the protective potential of ginseng against various neuronal insults. Potentiation of NGF by ginseng is also involved in other neuronal models. Nishiyama et al. (40) and Liao et al. (26) reported that ginsenosides increased neuronal survival and promoted neurite outgrowth of cultured chick embryonic dorsal root ganglia and cultured spinal cord neurons, respectively. Moreover, ginsenosides alleviated oxidative stress by scavenging of free radicals, inhibiting of NO production which usually accompanies glutamate excitotoxicity, inducing superoxide dismutase (SOD1) and catalase genes and reducing lipid peroxidation (24, 41 – 43). Also, it has been suggested that ginseng, in particular ginsenoside Rg3, inhibits both *N*-methyl-D-aspartate (NMDA) and non-NMDA glutamate receptors (44, 45) which contribute significantly to many neurological disorders particularly brain ischemia, trauma, stroke, and seizures (46 – 48). Inhibition of NMDA and non-NMDA receptors by ginsenosides resulted in a reduction of Ca^{2+} over-influx into neurons and thus protected cells from neurodegenerative processes evoked by Ca^{2+} overload (26, 49). These findings are in line with our recent results since we found that ginsenosides Rb1 and Rg1 increased the red/green fluorescence ratio of mitochondrial JC-1 staining in primary dopaminergic cell culture after glutamate treatment, indicating the possible role of both ginsenosides in attenuating mitochondrial depolarization induced by glutamate excitotoxicity and subsequent Ca^{2+} over-influx into mitochondria (28). Additionally, inhibition of Na^+ channels (50) and improved energy metabolism by retarding ATP breakdown in cultured neurons are also involved (51). Furthermore, some reports showed that neuroprotection by ginseng may be, in part, due to its effect on glial cell populations. In this respect, it has been reported that ginseng total saponins prevented astrocytic swelling induced by glutamate (52) and ginsenoside Rg1 inhibited microglial respiratory burst activity and decreased the accumulation of NO produced by activated microglia (53).

Modulatory effect of ginseng on neurotransmission

A number of studies have shown that some ginsenosides can modulate neurotransmission in the brain. Ginsenosides Rb1 and Rg1, the most abundant ginsenosides in ginseng root, can modulate acetylcholine release and re-uptake and the number of choline uptake sites, especially in the hippocampus (54). They also increase choline acetyltransferase levels in rodent brains (35, 55).

These results suggested that these compounds may improve central cholinergic function in humans and may be used to treat memory deficit (36). It has also been reported that ginsenosides increased dopamine and norepinephrine in the cerebral cortex (56), which may explain the favorable effects of ginseng extract upon attention, cognitive processing, integrated sensory-motor function, and auditory reaction time in healthy subjects (57). Additionally, it has been shown that ginseng total saponins can modulate dopaminergic activity at both pre-synaptic and post-synaptic receptors (58); and they can block behavioral sensitization induced by psychostimulants such as morphine (59), cocaine (58), methamphetamines (60), and nicotine (61 – 63). Furthermore, it was found that ginseng increased serotonin in the cortex (64), ginseng saponins raised the levels of biogenic amines in normal rat brain (65), ginsenoside Rg2 directly interacted with nicotinic receptor subtypes (66), and ginseng administration lead to regulation of GABAergic transmission in animals (67, 68).

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 (69, 70). For example, significant improvement in learning and memory has been observed in aged and brain-damaged rats after local administration of ginseng powder (71 – 73). In humans, Terasawa et al. (74) and D'Angelo et al. (57) have shown that ginseng or ginseng extract 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 (75). Consistent with the study of Kurimoto et al. (75), Wen et al. (5) demonstrated that red ginseng, ginseng powder, and ginsenoside Rb1 administration for seven days prior to ischemia rescued the hippocampal CA1 pyramidal neurons and subsequently ameliorated learning deficits in gerbils. Moreover, Shen and Zhang (76) suggested that the influence of ginsenoside Rg1 on the proliferating ability of neuronal progenitor cells may serve as an important mechanism underlying its nootropic and anti-aging effects particularly on learning and memory.

On the other hand, Persson et al. (77) have reported in a more recent study that regular use of ginseng during long periods of time (up to 2 years) by healthy participants did not provide any quantifiable beneficial effects on memory performance. This result coincides with the finding of Sorensen and Sonne (78) who reported that ginseng intake did not enhance memory functions.

Cardiovascular effects of ginseng

Ginseng has been shown to produce a number of actions on the cardiovascular system. Intravenous administration of ginseng to anesthetized dogs resulted in reduction, followed by an increase in blood pressure, and transient vasodilatation (79). In rats and rabbits, Lei and Chiou (80) and Kim et al. (81) found that extracts of *Panax notoginseng* decreased systemic blood pressure and ginsenosides exerted relaxing effects in rings of rat and rabbit aorta, respectively. This relaxing effect of ginseng and its active constituents on the cardiovascular system is partially due to the release of endothelial NO. Researchers have reported that chronic feeding of rabbits with ginsenosides may enhance indirectly vasodilatation by preventing NO degradation by oxygen radicals such as superoxide anions (82). Ginsenosides have depressant action on cardiomyocyte contraction which may be mediated, in part, through increased NO production (83). Korean red ginseng can improve the vascular endothelial dysfunction in patients with hypertension possibly through increasing NO (84). In addition to endothelium-derived NO release, Li et al. (85) reported that ginsenoside-induced vasorelaxation also involves Ca^{2+} activated K^{+} channels in vascular smooth muscle cells.

It has also been reported that crude saponin fractions of Korean red ginseng enhanced cerebral blood flow in rats (86) and ginsenosides reduced plasma cholesterol levels and the formation of atheroma in the aorta of rabbits fed on a high cholesterol diet (82). This anti-atherosclerotic action of ginseng components is apparently due to the correction in the balance between prostacyclin and thromboxane (87), inhibition of 5-hydroxytryptamine (5-HT) release from, and adrenaline and thrombin-induced aggregation of platelets (88), regulation of cGMP and cAMP levels, and prolongation of the time interval between conversion of fibrinogen to fibrin (89). Also, ginsenosides have been shown to be relatively potent platelet activating factor antagonists (90). In parallel with these findings, Nakajima et al. (91) concluded that red ginseng was found to promote the proliferation of vascular endothelial cells, to inhibit the production of endothelin which is known to constrict blood vessels resulting in raising blood pressure, and to increase the production of IL-1β, which suppresses the formation of thrombin in blood coagulation. In the same direction, Yuan et al. (92) used cultured human umbilical vein endothelial cells to conclude that American ginseng, *Panax quinquefolium L.* extracts,

significantly decreased endothelin concentration in a dose and time dependent manner after thrombin treatment.

The role of ginseng in angiogenesis has also been reported. Ginsenoside Rg1 promoted functional neovascularization into a polymer scaffold in vivo and tubulogenesis by endothelial cells in vitro (93). Therefore, ginsenoside Rg1 might be useful in wound healing as it can induce therapeutic angiogenesis.

Anti-inflammatory and anti-allergic effects of ginseng

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, pretreatment with ginsenoside Rg3 abrogated cyclooxygenase-2 expression in response to 12-*O*-tetradecanoylphorbol-13-acetate (TPA) in mouse skin, and ginsenosides Rb1 and Rc suppressed histamine and leukotriene release during the activation of guinea-pig lung mast cells in vitro (94 – 97). An additional anti-inflammatory action by ginseng has been mentioned by Li and Li (98). They reported that total saponins of Sanchi (*Panax pseudoginseng notoginseng*) reduced the level of the intracellular Ca^{2+} concentration in neutrophils and Kim et al. (99) found that ginseng had radioprotective effects against γ-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 (100). 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 (101 – 104). Hu et al. (105) reported that ginseng stimulated the immune system of dairy cows as it activated the innate immunity of cows and contributed to the cow's recovery from mastitis.

Anti-carcinogenic effect of ginseng

With respect to its anti-carcinogenic effects, it was reported that chronic intake of *Panax ginseng* C.A. MEYER decreased the incidence of cancers such as lung, gastric, liver, and colorectal tumors (106, 107). 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 (108 – 111). Ginsenosides Rb1, Rb2, and Rc inhibited tumor angiogenesis and metastasis (112), while ginsenoside Rh1 inhibited proliferation of the NIH 3T3 mouse fibroblast cell line (113).

Some of the mechanisms and processes underlying the above cited beneficial effects of ginseng against cancer have been stated by Surh et al. (114) and others. Using both in vivo and in vitro models, Surh et al. (114) reported that ginsenoside Rg3 treatment caused marked suppression of TPA-induced cyclooxygenase-2 (COX-2) expression in mouse skin and in human breast epithelial cells (MCF-10A). Also, he observed the same suppressive effect on NF-κB in mouse skin and extracellular regulated protein kinases (ERK) activation in TPA-stimulated MCF-10A cells. Consistent with the results of Surh et al. (114), Keum et al. (115) reported that 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 (116). ODC is a rate-limiting enzyme in the biosynthesis of polyamines that play a pivotal role in cell proliferation and tumor promotion (117). 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 E_2 (114). NF-κB 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 (118).

Aphrodisiac effect of ginseng

Ginseng effects on male sex behavior have been discussed recently by Murphy et al. (119), Nocerino et al. (1), and Murphy and Lee (14). In brief, it has been shown that ginseng is an essential constituent in traditional Chinese medicine for treatment of sexual impotence (1), and *Panax ginseng* and *Panax quinquefolium* enhanced male copulatory behavior in rats (119, 120). Consistently with these finding, Choi et al. (121) confirmed in a clinical study the efficacy of Korean red ginseng for erectile dysfunction in 30 patients. These positive aphrodisiac effects of ginseng may be attributed to the enhancement of nitric oxide release from endothelial cells of penile corpus cavernosum and consequent

relaxation (122). Furthermore, Fahim et al. (123) and Bahrke and Morgan (124) reported that *Panax ginseng* produced a dose-related increase in serum testosterone levels and American ginseng reduced the plasma level of prolactin hormone in rats. Testosterone might mediate the heightened copulatory behavior in ginseng-treated animals, while prolactin altered it. Taken together, these results suggest that both ginseng species may have direct actions on the anterior pituitary gland and/or on the hypothalamic dopaminergic mechanisms (14).

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 (125). It could also improve cardiac function in patients suffering from congestive heart failure (126). The authors have observed that the levels of serum cardiac troponin T (cTnT), a specific marker reflecting myocardial injury, was effectively reduced after treatment with the ginseng-containing Shenmai injection in congestive heart failure patients (126).

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 immunomodulatory 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 (127). Additionally, Li (128) has reported that 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 (128). 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 (129). It was further reported that 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 (130). Sparsely, ginseng has been reported to possess positive effects against herpes simplex type-II infections and diabetes mellitus, common cold symptom complex, ethanol-induced gastric lesion, and aspirin-induced gastric ulcers (131). Another study showed that ginseng helped postmenopausal women to alleviate climacteric syndromes, particularly fatigue, insomnia, and depression (132).

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 (36). Another important biological effect reported for *Panax ginseng* or its saponins is hypoglycemic and antihyperglycemic activity (133, 134). It has been shown that ginsenoside Rg1 increased the number of insulin receptors (135) and panaxan B, the main constituent of *Panax ginseng* for hypoglycemic activity, increased the plasma insulin level and enhanced insulin sensitivity (133). Ginseng also shows anti-stress activities against physical (i), chemical (ii), and biological (iii) stressful circumstances. For instance, i) it was shown that treatment with root saponins partially prevented the rectal temperature decline in normal rats exposed to cold stress (136), extracts of *Panax ginseng* had radioprotective effects or prolonged the survival time of irradiated mice (137, 138), and accelerated the hematological recovery of mice after x-ray irradiation (139) as well as reduced DNA damage in normal cells (140); ii) 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 (141, 142); and iii) *Panax ginseng* saponins-treated mice were found to be more resistant to infections by *Staphylococcus aureus*, *Escherichia coli*, and *Salmonella typhi* (143). Saponins attenuated the process of trypanosomiasis, prolonged the life span of the treated mice and delayed the appearance of trypanosomes in their blood (144). They also prevented the development of fever induced by typhoid and paratyphoid vaccines. Moreover, the aqueous extract of ginseng radix produced beneficial effects against gastritis and ginsenoside

Rb1 had an anti-ulcer effect through increasing mucus secretion (145).

Adverse effects and drug interaction of ginseng

The root of *Panax ginseng* appeared nontoxic to rats, dogs, and humans (146, 147). In inappropriate use, the most commonly experienced symptoms are hypertension, diarrhea, sleeplessness, mastalgia, eruptions, and vaginal bleeding (124, 148). Additionally, Siegel (149) described the term "ginseng abuse syndrome" after studying 133 users in Los Angeles. The author showed that the long term effects of the use of ginseng is characterized by hypertension, nervousness, sleeplessness, skin rash, diarrhea, confusion, depression, or depersonalization. Possible drug interactions have

Table 1. Important ginseng effects and its possible actions on different body systems

Subject	Ginseng effect(s)	Possible action(s)
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 vivo or in vitro	- Potentiates nerve growth factor - Anti-oxidative and anti-apoptotic mechanisms - Reduces lipid peroxidation - Inhibits excitotoxicity and Ca^{2+} over-influx into neurons - Maintains cellular ATP levels - Preserves structural integrity of neurons
	- Glial cells	- Prevents astroglial swelling - Inhibits microglial respiratory burst activity and NO production by activated microglia
	- Increasing cognitive performance (learning and memory)	- Modulates neurotransmission - Direct effect on hippocampal neurons
Cardiovascular system	- Antihypertensive	- Relaxes vascular smooth muscle cells through NO and Ca^{2+} mediated mechanisms - Inhibits production of endothelin which plays a role in blood vessel constriction
	- Anti-atherosclerotic effect	- Prevents platelet aggregation - Shows antagonistic action for platelet activity factor - Suppresses thrombin formation
	- Acceleration of wound healing	- Promotes functional neovascularization through endothelial proliferation
Inflammation and allergy	- Anti-inflammatory and anti-allergic effects	- Inhibits cytokine production such as IL-1β, IL-6, and TNF-α - Abrogates cyclooxygenase-2 gene expression - Suppresses histamine and leukotrienes release from mast cells - Stabilizes inflammatory cells such as neutrophils and lymphocytes - Antifibroblastic activity
Immune system	- Immunostimulant	- Enhances interferon induction, phagocytosis, natural killer cells, and B and T cells
Carcinogenesis	- Anti-carcinogenic effect	- Suppresses malignant transformation - Inhibits proliferation of tumor cells - Inhibits tumor invasiveness, metastasis, and angiogenesis
Aphrodisiac effect	- Enhancement of male copulatory behavior	- 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

been reported between *Panax ginseng* and warfarin, phenylzine, and alcohol (148).

Concluding remarks

To our understanding, the worldwide use of ginseng as a medical herb and its intake by many healthy individuals to invigorate their body functions (e.g., performance) are based primarily on i) its empirical history in contributing to recovery from a wide range of disease conditions particularly in Far East countries and ii) the results of recent experimental research that reported some of its beneficial effects in experimental animals. To date, there is a shortage of literature concerning clinical studies and the clinical use of ginseng to treat specific diseases in patients. Also, further research has to be considered to elucidate the definite pharmacological actions of ginseng and its constituents. In Table 1, the important effects of ginseng on different body systems and its possible actions are briefly summarized.

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