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Use of Ginseng in Medicine: Perspectives on CNS Disorders

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ABSTRACT

Ginseng, the root of Panax species, is a well-known folk medicine. It has been used as traditional herbal medicine in China, Korea and Japan for thousands of years and today is 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. Ginseng had been used primarily as a tonic to invigorate week bodies and help the restoration of homeostasis. However 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 actions on aging, CNS disorders and neurodegenerative diseases. In general, antioxidant, anti-inflammatory, anti-apoptotic and immunostimulant 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 which 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, Ginsenosides, CNS, Medicine, Chinese herbs*

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 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 root resemble the human body [1]. In China, ginseng roots are harvested when the plant is 3-6 years 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 prescriptions for 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]. They do not only believe that ginseng will engender physical benefits, but that it will also have positive effect on their 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

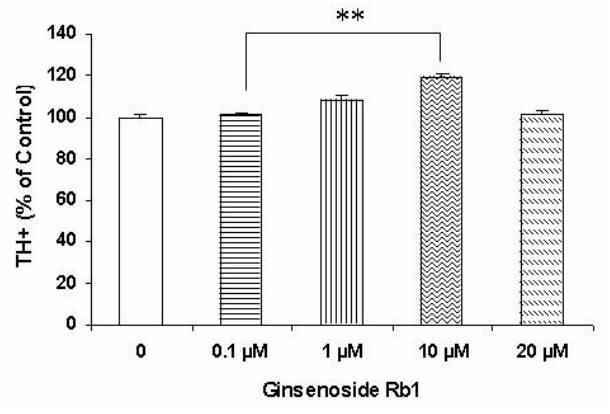

Fig 1. Effect of ginsenoside Rb1 on the survival of dopaminergic neurons. Ginsenoside Rb1 (0.1, 1, 10, 20 µM) was added to the cultures for six consecutive days (6th-12th DIV). About 100 % corresponds to the total number of TH+ neurons after 12 DIV in untreated controls. Values represent the mean ± SEM for three independent experiments with four wells in each treatment. Statistical differences were determined with Kruskal-Wallis (H)-test followed by $\chi 2$ test (**$p < 0.01$).

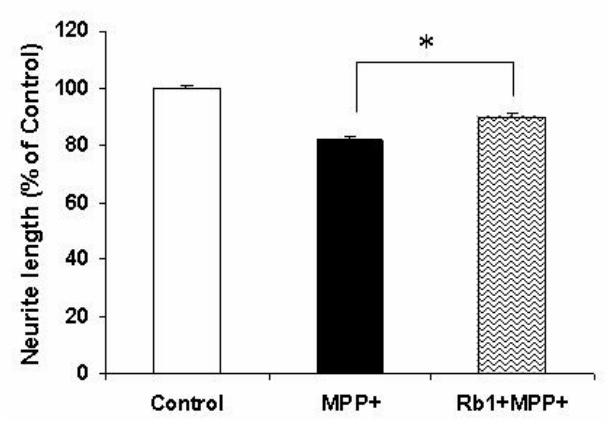

Fig 2. Effects of ginsenosides Rb1 on the neurite growth of MPP+-treated dopaminergic cells. Ginsenoside Rb1 (10 µM) was added on the 6th DIV for 6 consecutive days and the cultures were exposed to MPP+ (1 µM) on the 10th DIV for 48 h. Ginsenoside Rb1 significantly promoted the neurite growth of dopaminergic cells. 100% corresponds to neurite lengths (longest neurite/cell) of TH ir cells after 12 DIV in untreated control. Values represent the mean ± SEM for three independent experiments. Value of each experiment is the mean of the longest neurite of 30 cells in different four wells. Statistical differences were determined by the Wilcoxon test. (*$p < 0.05$).

exist in minute amounts and are believed to be responsible for most of ginseng's actions [10-13]. Additionally, ginsenosides operate by many mechanisms of action 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 glicosidic 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]. Interestingly, the ginsenoside content of ginseng can vary 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 medicines have received great importance and are recommended as natural alternatives to maintain one's health. Therefore, in this review we try to focus on the recently reported medicinal effects of ginseng and to summarize the results of different scientific studies using ginseng particularly in CNS disorders.

General Effects of Ginseng

Ginseng products are usually used as 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 central nervous system [21]. These effects include increased cell survival, extension of neurite growth and rescuing of neurons from death due to 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 to 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

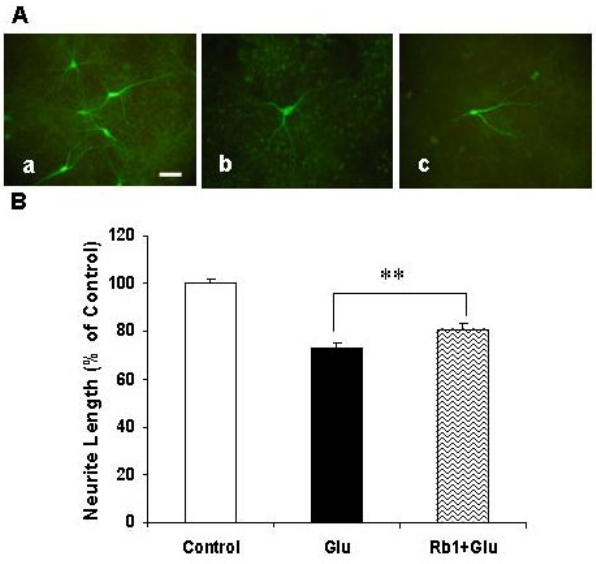

Fig 3. Effect of ginsenoside Rb1 on neurite growth of glutamate-treated dopaminergic cells. Ginsenoside Rb1 (10 μM) was added on the 6th DIV for 4 consecutive days followed by glutamate treatment (500 μM) for 15 min on the 10th DIV. Cultures were stained immunocytochemically after 12 DIV. **A**) Representative micrographs for dopaminergic cells labeled with fluorescent secondary antibody **a**) untreated control showing many dopaminergic cells with long branched neuritis **b**) glutamate-treated culture showing loss of some dopaminergic cells with shortened neuritis **c**) treatment of dopaminergic cell cultures with ginsenoside Rb1 increased the length of their neuritis compared with glutamate-treated neurons **B**) Ginsenoside Rb1 significantly increased the neurite growth of dopaminergic cells following glutamate treatment. 100 % corresponds to neurite lengths of TH^+ cells in untreated controls. Values represent the mean ± SEM of three independent experiments. Value of each experiment is the mean of the neurite lengths of 30 cells in four wells. Statistical differences were determined by Wilcoxon test (**$p < 0.01$).

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 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 *in vitro* studies, it has been shown that ginseng saponins enhanced neurite growth of the dopaminergic SK-N-SH neuroblastoma cells [27]. As mentioned above, we showed recently 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] (Fig 1, 2, 3). 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 could 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 effect against MPTP-induced apoptosis in the mouse substantia nigra. This anti-apoptotic effect 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 hydroxylse 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 the other neurodegenerative diseases. 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 been used for treatment of various neurodegenerative disorders including Alzheimer's disease, respectively.

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, inhibited NO production which usually accompanies glutamate excitotoxicity, induced superoxide dismutase (SOD1) and catalase genes and reduced 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 most neurological disorders [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

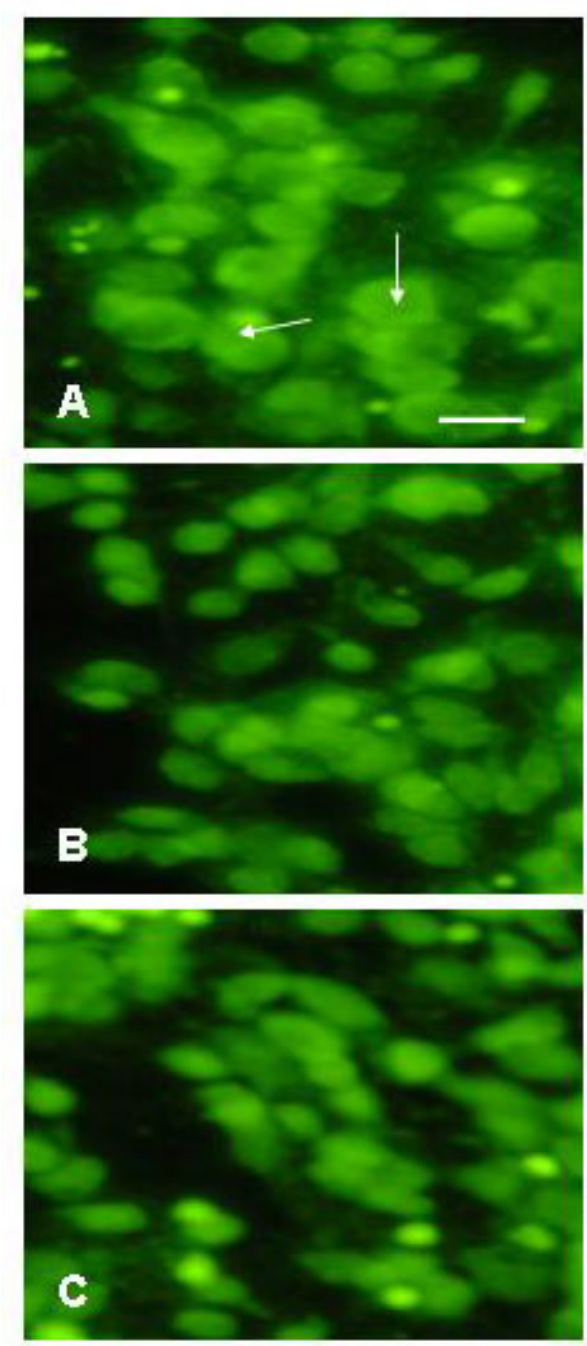

Fig 4. Fluorescent represenative micrographs showing the effect of ginsenoside Rb1 on Nissl's substances in glutamate-treated primary mesencephalic cell cultures. Nissl's substances found in the cell bodies and dendrites of neurons, but are abscent from axons. They consist principally of ribonucleic acid and nucleoprotien. They are concerned with protien synthesis and metabolism. Their condition varies with physiological and pathological conditions. Cultures were treated with ginsenoside Rb1 (10 μM) for 4 days (6^{th}-10^{th} DIV) followed by glutamate (500 μM) for 15 min on the 10^{th} DIV. Cultures were stained for Nissl's substances after 12 DIV **A**) untreated control culture showing intense fluorescence staining of Nissl's substances (arrows) **B**) treatment with glutamate decreased the fluorescence staining of Nissl's granules **C**) ginsenoside Rb1 treatment increased the intensity of Nissl's staining compared to glutamate-treated cells.

neurodegenerative processes evoked by Ca^{2+} overload [26, 49]. These findings are in line with our results in a recent study since we found that ginsenosides Rb1 and Rg1 increased 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^{+} channel [50] and improved energy metabolism by retarding ATP breakdown in cultured neurons and preservation structural integrity are also involved [51]. Furthermore, few reports showed that neuroprotection by ginseng may be, in part, due to its effect on glial populations. In this respect, it has been reported that ginseng total saponins prevent astrocytes 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. Both 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 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 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 individuals [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

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

Subject	Ginseng's 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 & 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, the number of insulin receptors and insulin sensitivity

effect of ginseng on cognition performance is owing 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 ischaemia 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 progenitors 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 period 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 re-

ported 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 anaesthetized 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 ginsenosides-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 antiatherosclerotic 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 conversions of fibrinogen to fibrin [89]. Also, ginsenosides have been shown to be relatively potent platelet activating factor antagonist [90]. In parallel with these findings, Nakajima et al. [91] found red ginseng 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 interleukin 1 beta, 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 studied. 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 12-0-tetradecanoylphorbol-13-acetate (TPA) in mice skin and ginsenosides Rb1 and Rc suppressed histamine and leukotrienes 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 pseudo-ginseng notoginseng) reduced the level of the intracellular Ca^{2+} concentration in neutrophils and Kim et al. [99] found that ginseng had radioprotective effect against γ-ray-induced DNA double strand breaks in cultured murine spleen lymphocytes. Furthermore, it was found that ginseng promoted apoptosis in renal interstitial fibroblasts and thus could affect renal interstitial fibrosis [100]. Ginseng also has immunostimulant effects as it enhances interferon induction, phagocytosis, natural killer (NK) cell, 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

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 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 former 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]. 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 is an essential early event prior to malignant transformation by inhibiting cell death signal activated by oncogenic Ras [118].

APHRODISIAC EFFECT OF GINSENG

Ginseng effects on 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]. Consistent 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].

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 protein (**Fig 4**) [36]. Another important biological effect reported for Panax ginseng or its saponins is hypoglycemic and antihyperglycemic activity [125, 126]. It has been shown that ginsenoside Rg1 increased the number of insulin receptors [127] and panaxan B, the main constituent of Panax ginseng for hypoglycemic activity, increased the plasma insulin level and enhanced insulin sensitivity [125]. 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 [128], extracts of Panax ginseng had radioprotective effects or prolonged the survival time of irradiated mice [129, 130] and accelerated the hematological recovery of mice after x-ray irradiation [131] as well as reduced DNA damage in normal cells [132], (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 [133, 134] and (iii) Panax ginseng saponins-treated mice were found to be more resistant to infections by Staphylococcus aureus , Escherichia coli and Salmonella typhi [135], saponins attenuated the process of trypanosomiasis, prolonged the life span of the treated mice and delayed the appearance of trypanosomes in their blood [136]. It 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 anti-ulcer effect through increasing mucus secretion [137].

ADVERSE EFFECTS AND DRUG INTERACTION OF GINSENG

The root of Panax ginseng appeared nontoxic to rats, dogs and humans [138, 139]. In inappropriate use, the most commonly experienced symptoms are hypertension, diarrhea, sleeplessness, mastalgia, eruptions and vaginal bleeding [124, 140]. Additionally, Siegel [141] described the term ginseng abuse syndrome after studying 133 users in Los Angeles. He has indicated 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 been reported between Panax ginseng and warfarin, phenelzine and alcohol [140].

CONCLUDING REMARKS

To our understanding, the worldwide spread of ginseng as a medical herb and its intake by many healthy individuals to invigorate their bodies are based primarily on (i) its empirical history in contributing to the recovery from a wide rang of disease conditions particularly in the Far East countries and (ii) the results of recent experimental research which reported some of its beneficial effects in experimental animals. To date, there is a shortage in the literature concerning the clinical use of ginseng to treat certain diseases in patients. Also, further research has to be considered to elucidate the definite pharmacological actions of ginseng and its constituents.

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