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Effects of *Panax ginseng* in Neurodegenerative Diseases

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Ginseng, the root of the *Panax ginseng*, has been a popular and widely-used traditional herbal medicine in Korea, China, and Japan for thousands of years. Now it has become popular as a functional health food and is used globally as a natural medicine. Evidence is accumulating in the literature on the physiological and pharmacological effects of *P. ginseng* on neurodegenerative diseases. Possible ginseng- or ginsenosides-mediated neuroprotective mechanisms mainly involve maintaining homeostasis, and anti-inflammatory, anti-oxidant, anti-apoptotic, and immune-stimulatory activities. This review considers publications dealing with the various actions of *P. ginseng* that are indicative of possible neurotherapeutic efficacies in neurodegenerative diseases and neurological disorders such as Parkinson's disease, Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis and multiple sclerosis.

Keywords: *Panax ginseng*, Ginsenosides, Neuroprotection, Neurodegeneration

INTRODUCTION

Panax ginseng Meyer is a perennial herb of the family *Araliaceae*. For millennia, *P. ginseng* has been traditionally used as a medicine in Asia, particularly in Korea, China and Japan. More recently, ginseng has become popular globally [1]. Its roots have been traditionally used to revitalize the body and mind, increase physical strength, prevent aging and increase vigor [2]. The main active pharmacological compounds in *P. ginseng* are ginsenosides, which are derivatives of triterpenoid dammarane. More than 31 ginsenosides has been isolated from natural and processed *P. ginseng*, and novel ginsenosides continue to be reported [3,4].

All ginsenosides have a common four-ring hydrophobic, steroid-like structure with attached sugar moieties. The specific action of each ginsenoside might depend on the diversity of the sugar components, and the number and position of the sugar moieties [5]. Each ginsenoside has different pharmacological effects, and a single ginsenoside can produce multiple effects in the same tissue [6,7]. Asian and Western scientists have introduced a new pharmacological concept of *P. ginseng*, with a wide range of actions on different body systems. Recently, ginsenosides have been shown to produce a number of beneficial effects in the nervous system [8-10].

NEUROPROTECTIVE EFFECTS OF *PANAX GINSENG*

Neuroprotection can be defined as a therapeutic intervention that prevents the death of vulnerable neurons, slows disease progression, and delays transition from the preclinical to the clinical stage [11]. Neuroprotection also refers to the inhibition or delay of neuronal death by virtue of the slowing or blocking of neuroprodegenerative processes either prematurely or in old age [12,13]. The possible influence of *P. ginseng* in neuroprotection is

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becoming increasingly recognized and researched.

Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disease that afflicts an estimated 2% of the global population over the age of 60 years. The mechanisms leading to PD rely on interactions between environmental and genetic factors, and are characterized by the accumulation and aggregation of misfolded α-synuclein. Neuropathological hallmarks are profound loss of dopaminergic neurons in the substantia nigra (SN) of the midbrain and accumulation of α-synuclein aggregates into Lewy bodies and Lewy neuritis [13]. The main symptoms of PD are motor disorders including tremor, rigidity, bradykinesia and postural instability, and non-motor-related disorders including sleep disturbance, autonomic dysfunction, cognitive deficits, depression, and olfactory deficits. These symptoms result from the progressive degeneration of the nigrostriatal dopaminergic pathway. To date, most PD therapies provide only symptomatic treatment, and no drug has been found that prevents the progressive loss of dopaminergic neurons in PD patients [14,15].

Ginseng extracts

Recently it has been demonstrated that *P. ginseng* and its pharmacologically active compounds, ginsenosides, have beneficial effects in both *in vitro* and *in vivo* models of PD (Table 1). For example, Hu et al. [16] reported that *P. ginseng* extracts can obviate cell death, curb the overproduction of reactive oxygen species (ROS), elevate the Bax/Bcl-2 ratio, stimulate the release of cytochrome C, and activate caspase-3 expression in 1-methyl-4-phenylpyridinium (MPP)(+)-treated SH-SY5Y human neuroblastoma cells. Van Kampen et al. [17] reported that the oral administration of *P. ginseng* extract G115 significantly and dramatically blocked tyrosine hydroxylase (TH)(+) cell loss in the SN and reduced the appearance

Table 1. Effect of *Panax ginseng* on Parkinson's disease

Components	Effect, materials and methods	Mechanism	References
Extract	(↓) MPP(+)-induced cytotoxicity in SH-SY5Y cells	(↓) ROS generation; (↓) elevated bax/bcl-2 ratio, release of cytochrome C and activation of caspase-3	16
	(↓) Locomotor dysfunction in MPTP/MPP(+)-induced C57BL/6 mice/SD rats	(↓) TH(+) cell loss in SN	17
Rg1	(↑) Dopamine and its metabolites contents in the striatum; (↑) TH expression in the SN of MPTP-induced C57BL/6 mice	(↓) MPTP-elevated iron levels, DMT1 expression; (↑) FP1 expression in the SN	18
	(↓) Rotational behavior induced by apomorphine in the 6-OHDA-induced Wister rats; (↓) TH(+) cell loss in SN	(↑) TH mRNA, dopamine transporter and bcl-2 protein	26
	Protect the SN neurons in MPTP-induced C57BL/6 mice	(↓) GSH reduction and T-SOD activation in SN; (↓) the phosphorylations of JNK and c-Jun	23
		(↑) Number of TH(+) neurons and TH expression (↓) Expression of p-ERK1/2 and iNOS	25
		(↑) TH(+) neurons; (↓) number of p-P38, COX-2, and PGE2(+)	27
	(↓) Apoptosis in dopamine-induced PC12 cells	(↓) The generation of ROS and the release of mitochondrial cytochrome C into the cytosol; (↓) the activation of caspase-3; (↓) iNOS protein level and NO production	24
	(↓) Cell death in rotenone-induced SN neurons	(↓) Cytochrome C release from the mitochrondrial membrane; (↓) the phosphorylation of Bad through activation of the PI3K/Akt pathway; (↑) MMP depletion	28
	(↓) Cytotoxicity in H_2O_2-induced PC12 cells	(↓) NF-κB signaling pathway as well as Akt and ERK1/2 activation	29
	(↓) Iron toxicity in 6-OHDA-treated MES23.5 cells	(↓) IRPs; (↓) cellular iron accumulation; (↓) Improper up-regulation of DMT1+IRE via IRE/IRP system	20
	(↓) Up-regulation of DMT1-IRE in MPP+-induced MES23.5 cells	(↓) Up-regulation of DMT1-IRE by MPP+ treatment (↓) ROS production and translocation of NF-kB to nuclei (↓) DMT1-mediated ferrous iron uptake and iron-induced cell damage by inhibiting the up-regulation of DMT1-IRE	19
Re	Protection from MPTP-induced apoptosis in the SN neurons	(↑) TH(+) neurons; (↓) TUNEL(+) cells (↑) Expression of bcl-2 protein and bcl-2 mRNA; (↓) expression of bax, bax mRNA, and iNOS; (↓) cleavage of caspase-3	30
Rd	(↓) Neurotoxicity in LPS-induced mesencephalic primary cultures	(↓) NO-formation and PGE2 synthesis	31

COX-2, cyclooxygenase-2; DMT1-IRE, divalent metal transporter 1 with iron responsive element; ERK, extracellular-signal-regulated kinases; GSH, glutathione; FP1, ferroportin1; iNOS, inducible nitric oxide synthases; IRPs, iron regulatory proteins; JNK, c-Jun N-terminal kinase; LPS, lipopolysaccharide; MMP, mitochondria membrane potential; MPP, 1-methyl-4-phenylpyridinium; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PGE2, prostaglandin E2; ROS, reactive oxygen species; SN, substantia nigra; TH, tyrosine hydroxylase; T-SOD, total superoxide dismutase; 6-OHDA, 6-hydroxydopamine.

of locomotor dysfunction in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)/MPP(+)-induced C57BL/6 mice and Sprague-Dawley (SD) rats. Thus, *P. ginseng* extracts appear to provide protective effects against neurotoxicity *in vitro* and *in vivo* models of PD.

Rg1

Rg1, one of the biologically active ingredients of *P. ginseng*, may be a candidate neuroprotective drug. Rg1 increases the contents of dopamine and its metabolites in the striatum as well as increasing TH expression in the SN of MPTP-treated C57BL/6 mice by attenuating elevated iron levels, decreasing divalent metal transport 1 (DMT1) expression, and increasing ferroportin1 expression in the SN [18]. Consistent with these *in vivo* observations, Rg1 attenuates DMT1 up-regulation and cellular iron uptake in the MPP+ or 6-hydroxydopamine-treated MES23.5 cells [19,20]. Elevated iron levels in the SN participate in neuronal death in neurodegenerative diseases including PD by enhancing the generation of free radicals and oxidative stress [21,22]. Suppressing oxidative stress mediates the neuroprotective effects of Rg1 in MPTP-induced SN [23,24]. Within 24 h following MPTP treatment, pretreatment of with Rg1 prevents the activation of glutathione reduction and total superoxide dismutase (SOD), and attenuates the phosphorylation of c-Jun, N-terminal kinase and c-Jun in SN of C57BL/6 mice [23]. Also, pretreatment with Rg1 markedly reduces the generation of dopamine-induced ROS and the release of mitochondrial cytochrome C into the cytosol and inhibits the activation of caspase-3, inducible nitric oxide synthase (iNOS) protein level and nitric oxide (NO) production in dopamine-induced PC12 cells [25]. Rg1 also can protect SN neurons by regulating the insulin-like growth factor-I receptor signaling pathway [24], the phospho (p)-extracellular signal regulated kinases (ERK)1/2, and p-p38 mitogen-activated protein kinases (MAPKs) signaling pathways [26,27].

Recently, Leung et al. [28] reported that Rg1 has neuroprotective effects for primary SN neurons against rotenone toxicity, because Rg1 prevents cytochrome C release from the mitochrondrial membrane and increases the phosphorylation inhibition of the pro-apoptotic protein Bad through the activation of the phosphoinositide-3-kinase (PI3K)/Akt pathway. More recently, Liu et al. [29] proved that pretreatment with Rg1 can markedly reduce the cytotoxicity induced by hydrogen peroxide (H_2O_2) in PC12 cells by inhibiting nuclear factor-kappa B (NF-κB) activation. In their study, the NF-κB signaling pathway was thoroughly activated by H_2O_2 in PC12 cells and pretreatment with Rg1 suppressed phosphorylation and nuclear translocation of NF-κB/p65, and phosphorylation and degradation of inhibitor protein of κB (IκB) as well as the phosphorylation of IκB-kinase complex. Rg1 also inhibited the activation of Akt and the ERK1/2. Furthermore, the protection of Rg1 on H_2O_2-injured PC12 cells was attenuated by pretreatment with two NF-κB pathway inhibitors (JSH-23 or BOT-64) [29].

Re and Rd

Re and Rd have neuroprotective effect in neurotoxicity of SN. Pretreatment with Re has been reported to markedly increase TH(+) neurons and to decrease the terminal deoxynucleotidyl transferase dUTP nick end labeling(+) ratio compared with MPTP-treated wild type mice. Furthermore, Re enhances the expression of bcl-2 protein and bcl-2 mRNA, but reduces the expressions of bax, bax mRNA, and iNOS, and weakens the cleavage of caspase-3 [30]. In addition, Rd inhibits loss of dendritic processes, changes in the perikarya, cellular atrophy and neuronal cell loss of TH(+) cells in mesencephalic primary cultures treated with lipopolysaccharide (LPS) by reducing NO-formation and PGE2 synthesis [31]. Thus, *P. ginseng* and its various elements may provide a potential means of slowing the progress of PD.

Alzheimer's disease

Alzheimer's disease (AD), the most common cause of dementia in elderly people, is a neurodegenerative disease characterized by senile plaque deposition, neurofibrillary tangle formation, and neuronal loss. The key mechanism leading to AD pathogenesis is the abnormal metabolism of amyloid precursor protein (APP) [32,33]. The AD brain is characterized by a variety of alterations in cellular and molecular mechanisms, including amyloid beta (Aβ) clearance capability, mitochondrial function, synaptic dysfunction, down-regulation of anti-oxidant, up-regulation of oxidative stress, and inflammatory response [34-36]. Most therapeutic strategies for AD only provide symptomatic treatment, including inhibition of generation or aggregation of Aβ, enhancement of the removal of Aβ from the neurons, interruption of tau hyperphosphorylation, and the use of more efficacious anti-oxidant and anti-inflammatory drugs [37-39]. However, no drug has yet been found to prevent the progressive loss of neurons in AD patients [32-39].

Extracts

Recent evidence has shown the effectiveness of *P. ginseng* extract and powder and various ginsenosides

Table 2. Effect of *Panax ginseng* on AD

Components	Effects, materials and methods	Mechanism	References
Powder	(↑) Cognitive performance of AD patients	(↑) Cognitive subscale of ADAS and MMSE	41
Extract	(↑) Cognitive subscale of ADAS and CDR after 12 wk of KRG therapy (9 g/d)		40
	(↓) Memory loss in aged SAMP8 mice with ginsenoside consumption (100 or 200 mg/kg/d) in drinking water for 7 mo	(↓) Oxidative stress; (↑) plasticity-related proteins (PSD-95, p-NMDAR1, p-CaMKII, p-PKA Cβ, PKCγ, p-CREB and BDNF) in hippocampus	42
	Neuroprotective effects in cyclosporine A-treated human neuroblastoma cells SY5Y cells	(↑) Calcineurin activity; (↓) tau phosphorylation	43
Rb1	(↓) Aβ25-35-induced tau hyperphosphorylation in cortical neurons	Involvement of calpain and p25 of CDK5 pathway	47
	(↓) Aβ1-42-induced neurotoxicity in cortical neurons	(↓) LDH release, and MDA product; (↑) SOD activity	44
	(↓) Aβ25-35-induced neurotoxicity in PC12 cells	(↓) ROS overproduction and lipid peroxidation; (↑) Bcl-2/Bax and caspase-3 activation	45
	(↓) Aβ1-42-induced neurotoxicity in primary cortical neuron culture	(↓) Tau hyperphosphorylation; (↑) levels of p-Ser(473)-Akt; (↓) GSK-3β activity by PI3K activation	46
	Anti-neuroinflammation effect in an Aβ1-42 treated rat model of AD	Reverse the changes of COX-2, IkB-α and nNOS in the hippocampus	48
	(↓) LPS-induced primary microglial activation from rats	(↓) NO and proinflammatory cytokines (IL-1β, IL-6, and TNF-α); (↓) Expression of bcl-2 and bax	59
Rg1	(↓) Aβ25-35-induced learning and memory impairment	(↓) Cortical and hippocampal ChAT activity decline; (↓) activity of AchE	60
	(↓) Neuronal damage by Aβ25-35-induced microglias	(↓) Toxicity of Aβ and/or IFN-γ to microglias; (↓) microglial respiratory burst activity; (↓) accumulation of NO	58
	The role of anti-dementia in okadaic acid (OA, 1 μM) treated brain slices model of AD from 5-week-old rat	(↓) Expression of p-tau; (↓) formation of neurofibrillary tangles; (↑) expressions of NR1 and NR2B	56
	(↓) Expression of p-tau induced by okadaic acid in rat brain slices	(↑) Expressions of tau and PP2A proteins	57
	(↓) Aβ42-induced apoptosis in CHO cells transfected with mutant PSM146L/APP751 cells	(↑) Cytoactivity; (↓) protein expression levels of Aβ42 and caspase-3	50
	(↓) Expressions of p-tau and caspase-3 in brain slices from AD model rats		49
	(↑) Learning and memory impairments and neuronal apoptosis induced by DEX in 12-month-old male mice	(↓) mRNA level of caspase-3; (↓) protein expression of caspase-3 and cytochrome C; (↓) activity of caspase-9 and caspase-3	52
	(↓) H_2O_2-induced cytotoxicity in PC12 cell	(↓) NF-kB signaling pathway (p-NF-kB/p65, p-IkB and p-IKK); (↓) Akt and ERK1/2 activation	29
	(↑) LPS-treated primary microglial activation from rats	(↑) NO and proinflammatory cytokines (IL-1β, IL-6, and TNF-α); (↑) Expression of Bcl-2 and Bax	59
	(↑) Learning and memory outcomes in SAMP8 mice	(↓) Hippocampal Aβ content, PKA RIIα level (isoform IIα of the regulatory subunit of PKA); (↑) p-CREB and BDNF levels	53
	(↓) Aβ-induced cytotoxicity in PC12 cells.	(↓) Cell death, LDH release, NO release, ROS production, lipid peroxidation, intracellular Ca^{2+} elevation, and apoptosis; (↓) β-secretase activity	55
	(↓) Levels of the Aβ40 and Aβ42 in conditioned medium of CHO 2B7 cells and in the brains of Tg2576 mice		54
Rg2	(↓) Glutamate-induced neurotoxicity in PC12 cells	(↑) Cell viability; (↓) intracellular Ca^{2+} concentration, lipid peroxidation (the excessive production of MDA, NO) and the protein expression levels of calpain II, caspase-3 and Aβ1-40	60
Rg3	(↓) Levels of Aβ40 and Aβ42 in SK-N-SH cells transfected with SweAPP	(↑) NEP gene expression	64
	(↓) Levels of the Aβ40 and Aβ42 in conditioned medium of CHO 2B7 cells and in the brains of Tg2576 mice		54
Rh2	(↓) Aβ-induced toxicity in astrocytes	(↑) PACAP gene expression	65
Re	(↓) Levels of the Aβ40 and Aβ42 in conditioned medium of CHO 2B7 cells and in the brains of Tg2576 mice		54

AD, Alzheimer's disease; Aβ, amyloid beta; AchE, acetylcholinesterase; ADAS, Alzheimer's disease assessment scale; Bax, Bcl-2–associated X protein; Bcl-2, B-cell lymphoma 2; BDNF, brain-derived neurotrophic factor; CaMKII, Ca^{2+}/calmodulin-dependent protein kinases II; ChAT, choline acetyltransferase; CDK5, cell division protein kinase 5; CDR, clinical dementia rating; COX-2, cyclooxygenase-2; CREB, cAMP response element-binding; DEX, dexamethasone; ERK, extracellular-signal-regulated kinases; GSK-3, glycogen synthase kinase-3; IFN-γ, interferon-gamma; IkB, inhibitor of kB; IKK, IkB kinase; IL, interleukin; K-MMSE, Korean version of the mini-mental status examination; LDH, lactate dehydrogenase; LDH, lactate dehydrogenase; LPS, lipopolysaccharide; MDA, malondialdehyde; MMSE, mini-mental state examination; NEP, neprilysin; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; NMDAR1, N-methyl-D-aspartate receptor 1; nNOS, neuronal nitric oxide synthases; NO, nitric oxide; NR, N-methyl D-aspartate receptor; PACAP, pituitary adenylate cyclase-activating polypeptide; PKA RIIα, isoform II alpha of the regulatory subunit protein kinase A; PKC, protein kinase C; PP2A, protein phosphatase 2A; PSD-95, postsynaptic density protein 95; ROS, reactive oxygen species; SAMP8, senescence-accelerated mouse prone 8; SweAPP, Swedish mutant β-amyloid precursor protein; TNF-α, tumor necrosis factors-α.

on AD using *in vitro* and *in vivo* models (Table 2) [40-43]. Patients receiving Korean red ginseng powder (9.0 g/d) or Korean white ginseng powder (4.5 g/d) showed significant improvement on the AD assessment scale, the mini-mental state examination scores, and the clinical dementia rating after 12 wk of ginseng therapy when compared with those in the control group [40,41]. Long-term (for 7 mo) consumption of ginseng total saponins (100 and 200 mg/kg/d) demonstrated significant prevention of the memory loss in aged senescence-accelerated mouse prone 8 (SAMP8) mice by decreasing oxidative stress and up-regulating plasticity-related proteins that include postsynaptic density protein 95, p-*N*-methyl-D-aspartic acid receptor 1 (p-NMDAR1), p-Ca^{2+}/calmodulin-dependent protein kinases II, p-protein kinase A (p-PKA) catalytic β subunit, p-protein kinase Cγ subunit, p-cyclic adenosine monophosphate (p-cAMP), p-cAMP response element-binding (p-CREB), and brain derived neurotrophic factor (BDNF) in the hippocampus [42]. It also has been suggested that *P. ginseng* extracts bestow neuroprotection by regulating the phosphatase activity of purified calcineurin and tau phosphorylation in SY5Y human neuroblastoma cells [43]. Calcineurin, a Ca^{2+}/calmodulin-dependent protein phosphatase, plays an important role in tau hyperphosphorylation, which is one of the neuropathologic features in the brains of AD patients [43].

Rb1

In vitro, Rg1 protects neurons against the neuronal toxicity (shrunken perikaryon with loss of neurite processes) of Aβ1-42, most likely through an anti-oxidant pathway; Lactate dehydrogenase release, malondialdehyde (MDA) production, and SOD activity in Aβ1-42-treated neurons were all markedly decreased [44]. Pretreatment with Rb1 for 24 h inhibits Aβ25-35-induced ROS overproduction and lipid peroxidation in PC12 cells, and increases bcl-2/bax and caspase-3 activation, thereby improving cell survival [45]. Pretreatment with Rb1 significantly attenuates Aβ1-42 or 25-35-induced neurotoxicity and tau hyperphosphorylation both *in vivo* and *in vitro* [46,47]. Rb1 also increases the levels of p-Ser (473)-Akt and down-regulates glycogen synthase kinase-3β activity by activation of PI3K [46]. Consistent with these reports, Rb1 attenuates the mRNA levels of calpain and p25 of cell division protein kinase 5 pathway in primary cultured cortical neurons [47], and Rb1 reverses the changes in several direct or indirect neuroinflammation markers (COX-2, IkB-α, and neuronal NOS) at multiple AD-related sites in primary cortical neurons [48].

Rg1

Rg1 inhibits the activation of NF-κB/p65, Akt and the ERK1/2 in H_2O_2-induced PC12 cells [29]. Rg1 also inhibits the expression of caspase-3 to obviate apoptosis in brain slices from AD model rats [49] and in Chinese hamster ovarian tumor cells transfected with mutant PSIM146L gene and WT APP751 gene (mutant PSM146L/APP751 cells) stably producing excessive Aβ1-42 [50]. Consistent with these reports, Wang et al. [51] reported that treatment with Rg1 (5 and 10 mg/kg, for 10 d) ameliorates the Aβ25-35-induced learning and memory impairment by preventing the cortical and hippocampal choline acetyltransferase activity decline induced by Aβ25-35, and by inhibiting the activity of acetylcholinesterase [51]. And Li et al. [52] reported that treatment with Rg1 (6.5 mg/kg, for 21 d) improves learning and memory by downregulating the mRNA level of caspase-3, decreasing the expressions of caspase-3 and cytochrome C in the hippocampus and neocortex, and inhibiting the activity of caspase-9 and caspase-3 in 12-month-old male mice chronically treated with stressful levels of dexamethasone.

Long-term consumption (for 3 months) of Rg1 could attenuate hippocampal Aβ contents and improve learning and memory outcomes in SAMP8 mice by decreasing PKA RIIα level (isoform IIα of the regulatory subunit of PKA) and increasing p-CREB and BDNF levels in the hippocampus [53]. Rg1 reduces Aβ42 levels in cell-based assays and in the brains of Tg2576 mice, a mouse model of Aβ accumulation [54]. Rg1 protects Aβ25-35-induced cytotoxicity in PC12 cells by inhibiting β-secretase activity [55]. Also, high-dose Rg1 (240 μM) decreases the expression of p-tau and increases the expressions of NMDAR1 and NMDAR2B in okadaic acid-treated brain slices in a 5-week-old Wister rat model of AD [56,57].

Gong and Zhang [58] showed that Rg1 could prevent the toxicity of Aβ25-35 and/or interferon (IFN)-γ to microglia, inhibit microglial respiratory burst activity and decrease the accumulation of NO. The results are consistent with a neuroprotective effect of Rg1 against damage by reactive microglia in AD. Interestingly, Joo et al. [59] discovered that Rb1 and Rg1 exert opposite effects in a dose-dependent manner (50-250 μg/mL). In their report, whereas Rg1 stimulated NO and the proinflammatory cytokines interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α in LPS-treated primary microglial cultures from rats, Rb1 exerted a significant inhibitory effect on this proinflammatory repertoire [59]. Moreover, when a combined treatment with equal doses of Rb1 and Rg1 was given, Rb1 significantly counteracted the stimulatory effects of Rg1 for 72 h, as evidenced by NO assay results [59]. These results suggest that neurodegenerative diseases such as AD, which are caused primarily by cell death due to chronic inflammation and cell stress, might be controlled by proper doses of non-toxic, natural Rg1 and Rb1 [59].

Rg2

Rg2 is a protopanaxatriol-type compound that is one of the major active components in the root and stem leaves of *P. ginseng*. It has been suggested that Rg2 acts by a wide range of mechanisms [60,61]. Rg2 attenuates glutamate-induced neurotoxicity in PC12 cells as judged by decreased the cell viability, increased intracellular Ca^{2+} concentration, lipid peroxidation (i.e., excessive production of MDA and NO), and the protein expression levels of calpain II, caspase-3, and Aβ1-40 [60]. It also has been reported that Rg2 protects from memory impairment via anti-apoptosis in a rat model of vascular dementia [61].

Rg3

Microglia are phagocytic cells that are the major inflammatory response cells of the central nervous system (CNS). They have important pathophysiologic roles in AD in both potentially neurotoxic responses and potentially beneficial phagocytic responses [62]. Joo and Lee [63] examined whether Rg3 enhances the microglial phagocytosis of Aβ. They found that Rg3 promotes Aβ uptake, internalization, and digestion. Increased maximal Aβ uptake was observed at 4 and 8 h after pretreatment with Rg3, and the internalized Aβ was almost completely digested from cells within 36 h. In the report, the expression of type A macrophage scavenger receptor (MSRA) was also up-regulated by Rg3 treatment in dose- and time-dependent manners in the cytosol. The authors suggested that microglial phagocytosis of Aβ may be enhanced by Rg3, that the effect of Rg3 on promoting clearance of Aβ may be related to the MSRA-associated action of Rg3, and that stimulation of the MSRA might contribute to the therapeutic potentials of Rg3 in microglial phagocytosis and digestion in the treatment of AD [63]. Moreover, it was has been reported that Rg3 significantly reduces the levels of Aβ40 and Aβ42 in SK-N-SH cells transfected with Swedish mutant β-amyloid precursor protein by enhancing neprilysin gene expression, the rate-limiting enzyme in the Aβ degradation in the brain [64].

Re and Rh2

It has been reported that reactive astrocytes induced by Aβ contributes to disease progression in AD [62]. Shieh et al. [65] found that Rh2 stimulates the gene expression of the neurotrophic factor, pituitary adenylate cyclase-activating polypeptide to promote cell survival and cell proliferation in type I rat brain astrocytes. The results suggest that Rh2 attenuates Aβ-induced toxicity. Chen et al. [54] reported that Re reduces significantly Aβ42 levels in cell-based assays and oral administration reduces significantly Aβ levels in the brains of Tg2576 mice. Thus, *P. ginseng* itself and its various constituents may provide a potential means of slowing the progress of AD.

Gintonin

Recently, gintonin, newly identified compounds from ginseng, is novel lysophosphatidic acids-protein complexes and activates G protein-coupled lysophosphatidic acid receptors with high affinity [66]. Hwang et al. [67] investigated the effect of gintonin using *in vitro* and *in vivo* models in AD. In the study, gintonin promoted sAβPPα release in concentration- and time-dependent manners and decreased Aβ1-42 release and attenuated Aβ1-40-induced cytotoxicity in SH-SY5Y cells. Gintonin also rescued Aβ1-40-induced cognitive dysfunction in mice. Moreover, in a transgenic mouse AD model, long-term oral administration of gintonin attenuated amyloid plaque deposition as well as short- and long-term memory impairment [67]. These results suggest that gintonin could be a useful agent for AD prevention or therapy.

Huntington's disease

Huntington's disease (HD) is a hereditary neurological disorder of the CNS that causes progressive degeneration of striatal cells in the brain. HD is characterized clinically by involuntary abnormal movements, psychiatric disturbance, and cognitive deficit and pathologically by degeneration of the gamma-aminobutyric acid-ergic medium size spiny neurons [68]. HD originates due to the mutation of the gene encoding the huntingtin (htt)-protein. The underlying genetic mutation has been identified as a CAG-repeat expansion in the IT15 gene of chromosome 4 [69]. The formation of mutant htt protein leads to mitochondrial dysfunction, caspase activation, apoptosis, excitotoxicity, and RNA dysregulation. Recent evidence suggests that microglial activation is also an integral part of HD pathogenesis [70,71]. However, the exact mechanisms linking the formation of the mutant htt protein to neuronal cell death in the striatum are unclear [72]. There are no current drug therapies proven to help ameliorate or abrogate the disease process in HD.

Table 3. Effect of *Panax ginseng* on HD, amyotrophic lateral sclerosis, and multiple sclerosis

Disease	Components	Effects, materials and methods	Mechanism	References
HD	Extract	Improve systemic 3-NP-induced behavioral impairment and extended survival in rat	No effect on the inhibition of succinate dehydrogenase activity; (↓) 3-NP-induced intracellular Ca^{2+} elevations and cytotoxicity of striatal neurons	73
	Rb1, Rb5 Rc	(↓) Glutamate-induced apoptosis in YAC128 medium spiny neurons	(↓) Glutamate-induced Ca^{2+} responses in cultured MSN	74
ALS	Rb2	(↑) Transcriptional activation of the Cu, Zn-superoxide dismutase gene	(↑) Induction of the SOD1 gene; (↑) specific binding of the AP2 transcription factor	89
MS	Polysaccharides	(↓) Encephalitogenic response during EAE	(↓) The proliferation of autoreactive T cells and the production of IFN-γ, IL-1β and IL-17; (↑) the generation of immunosuppressive regulatory T cells (Tregs) through the activation of transcription factor, Foxp3	97

ALS, amyotrophic lateral sclerosis; AP2, activating protein 2; EAE, experimental autoimmune encephalomyelitis; HD, Huntington's disease; IFN-γ, interferon-gamma; IL, interleukin; MS, multiple sclerosis; MSN, medium spiny striatal neuronal cultures; SOD1, superoxide dismutase 1; 3-NP, 3-nitropropionic acid.

Ginseng total saponins

Ginseng total saponins (GTS) and its compounds, which are the major active ingredients of *P. ginseng*, have protective effects against neurotoxin insults (Table 3) [73,74]. To test the neuroprotective activity of GTS and its compounds, Kim et al. [73] examined the *in vitro* and *in vivo* effects of GTS on striatal neurotoxicity induced by repeated treatment of the succinic dehydrogenase inhibitor 3-nitropropionic acid (3-NP) in rats. Because administration of 3-NP induces a selective striatal pathology similar to that seen in HD, it has been widely used as an animal model of HD [75,76]. Kim et al. [73] reported that systemic administration of GTS can significantly improve 3-NP-induced behavioral impairment and extend the survival of SD rats. To explain the mechanisms underlying the *in vivo* protective effects of GTS against 3-NP-induced striatal degeneration, the authors examined the *in vitro* effect of GTS against 3-NP-mediated cytotoxicity using cultured rat striatal neurons. GTS inhibited 3-NP-induced elevation of intracellular Ca^{2+} concentration and restored the 3-NP-induced mitochondrial transmembrane potential reduction in cultured rat striatal neurons. As well, the authors reported that GTS prevented 3-NP-induced striatal neuronal cell deaths in a dose-dependent manner [73]. The results suggest that the *in vivo* protective effects of GTS against 3-NP-induced rat striatal degeneration might be achieved by inhibition of 3-NP-induced intracellular Ca^{2+} elevations and cytotoxicity of striatal neurons.

Recently, activated microglia have been proposed to play a major role in the pathogenesis of a range of neurodegenerative diseases including HD [71,77]. And GTS and Rh1 have been reported to have an anti-inflammatory mechanism in LPS-stimulated microglia [78,79]. Based on these results, we studied whether *P. ginseng* extract has a neuroprotective effect in 3-NP-stimulated striatal toxicity of mice. We confirmed that pretreatment (for 10 d) and co-treatment (before 1 h) with *P. ginseng* extract improved clinical behavior and striatal neuronal death by regulating microglial activation, inflammatory mediators (iNOS, TNF-α, IL-6, and IL-1β), and activation of p38 and ERK1/2 MAPKs signaling pathways (unpublished).

Ginsenosides

To assess the neuroprotective activity of compounds of GTS, Wu et al. [74] tested 10 different ginsenosides in a previously developed *in vitro* HD assay with primary medium spiny striatal neuronal cultures (MSN) from a YAC128 HD mouse model. Pretreatment with Rb1 (0.01-0.1 μM), Rc (0.01 μM), and RG5 (1.0 μM) effectively protected YAC128 medium spiny neurons from apoptosis induced by 250 μM glutamate. However, the other seven ginsenoside samples (Rd, Re, Rg3, Rh1, mixture of Re and Rd, mixture of Rk1 and Rg5, and mixture of Rh4 and Rk3) had no protective effects on glutamate-induced apoptosis of YAC128 MSN at the concentrations tested and Re, Rh1, and mixture of Rk1 and Rg5 were actually toxic to MSN at 1 μM [74]. From further experiments, the authors suggested that the neuroprotection bestowed by Rb1, Rc, and Rg5 could correlate with their ability to inhibit glutamate-induced Ca^{2+} responses in cultured MSN [74]. From these results, the authors concluded that Rb1, Rc, and Rg5 offer a potential therapeutic choice for the treatment of HD and possibly other neurodegenerative disorders [74].

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS), also referred to as Lou Gehrig's disease and motor neuron disease, is a disease of the motor nervous system caused by the degeneration of upper and lower neurons, located in the ventral horn of the spinal cord and cortical neurons that provide their efferent input. ALS is characterized by rapidly progressive weakness, muscle atrophy and fasciculations, spasticity, dysarthria, dysphagia, and respiratory compromise. Sensory function generally is spared, as are autonomic and oculomotor activity [80-83]. ALS is a progressive and neurodegenerative disease with most affected patients dying of respiratory compromise and pneumonia within 2 to 3 yr after the onset of symptoms [84]. Familial cases of ALS are known, but most cases of ALS (>90%) are sporadic and are likely caused by multi-factorial factors [85,86], although the causes and underlying mechanisms are not completely understood. Many ALS patients use unconventional or alternative therapies, of uncertain efficacy or toxicity. One example is ginseng root, long used in natural or traditional therapies for a variety of ailments. The herbal remedies, *P. quinquefolium*, *P. japonicus*, and Rb2 have recently been demonstrated to possess neuroprotective and neurotrophic properties [87-90], which may be useful *in vivo* and *in vitro* models of ALS.

Panax quinquefolium/japonicus and ginsenosides

In a study using mutant SOD1 transgenic mice [B6SJL-TgN(SOD-1G93A)1Gur], the relevant animal model for ALS, it was reported that crude ginseng powder from *P. quinquefolium* significantly delay the onset of signs (116 d *vs*. 94 d) of motor impairment and prolong the survival (139 d *vs*. 132 d) of mice [87] and that saponins from *P. japonicus* protect against alcohol-induced hepatic injury in mice by up-regulating the expression of glutathione peroxidase 3, SOD1 and SOD3 [88]. It has been demonstrated that Rb2 can significantly activate Cu, Zn-SOD gene 1 through the transcription factor activating protein 2-binding site in human HepG2 hepatoma cells (Table 3) [89] and that Rb1 protects endothelial cells from H_2O_2-induced cell senescence by modulating redox status [90]. However, the protective effect of *P. ginseng* and ginsenosides in ALS are still unclear.

Multiple sclerosis

Multiple sclerosis (MS) is a chronic immune-mediated inflammatory demyelinating and neurodegenerative disorder of the CNS. It constitutes the most common nontraumatic cause of neurological disability among young adults and there is an increasing female predominance in North America and Western Europe. Partially known genetic and environmental factors constitute the etiology, which characterize complex genetic diseases [91-93]. Symptoms of MS commonly include physical (visions, balance problems and dizziness, fatigue, bladder problems, and stiffness and/or spasms), sensory, memory, cognitive, emotional, and sexual problems [91-93]. Numerous studies have directly led to the development of three medications approved for MS: IFN-β, glatiramer acetate, and the combination of mitoxantrone and natalizumab [94]. However, these drugs have limited therapeutic effect in stopping the onset and progression of MS and also have several other drawbacks that include cost, the need for intramuscular or subcutaneous injection, and occasionally infection/irritation after injection [95]. Developing an effective new drug would be of great clinical benefit in the prevention and treatment of MS.

Ginsan extracts

An acidic polysaccharide of *P. ginseng* (APG), commonly called ginsan, is a purified acidic polysaccharide extracted from the roots of *P. ginseng* (Table 3) [96]. Recently, Hwang et al. [97] demonstrated that APG significantly ameliorated the severity of experimental autoimmune encephalomyelitis (EAE), the animal model for human MS, by inhibiting the proliferation of autoreactive T cells as well as the production of the inflammatory cytokines, IFN-γ, IL-1β and IL-17. More importantly, the depletion of $CD25^+$ cells abrogated the beneficial effects of APG treatment in mice with EAE. The authors also investigated whether APG could promote the generation of immunosuppressive regulatory T cells (Tregs) through the activation of the transcription factor, Foxp3 [97]. Based on these results, we are studying whether *P. ginseng* extract has a neuroprotective effect in myelin oligodendrocyte glycoprotein-stimulated EAE model of mice. We confirmed that pretreatment with *P. ginseng* extract can delay the onset of clinical behavior and improve the severity of EAE (unpublished). However, it also has been reported in a single-center, randomized, double-blind, and placebo-controlled crossover pilot study that American ginseng does not improve fatigue in MS [98]. The study examined the safety and efficacy of an escalating dose (100, 200, and 400 mg/d) of American ginseng over 6 wk in 56 subjects with MS and fatigue. There were no serious adverse events but fatigue in American ginseng group, as assessed by the fatigue severity scale, was not significantly different from fatigue in the placebo group.

CONCLUSION

P. ginseng has been used for thousands of years as a traditional medicine in Asian countries. *P. ginseng* has extensive pharmacological actions and specific mechanism in the CNS. The major active ingredients of *P. ginseng*, ginsenosides, exhibit anti-inflammatory, anti-oxidant, and anti-apoptotic mechanisms and exert various effects involving stress and the immune system in the nervous system. Rd, Re, and Rg1 are effective in treatment of PD and Rb1, Rg1-3, Re, and Rh2 are effective in the treatment of AD. Based on the increasing literature regarding neuroprotective effects, *P. ginseng* and ginsenosides may potentially be useful as dugs for the treatment of PD and AD. However, how these neuroprotective effects relate to the structures of the ginsenoside is still not yet fully understood. Further neurological studies should include the mechanisms of action in more detail with emphasis on specificity and the relationship between structure and function. The prevalence of HD, ALS, and MS are also increasing. However, little is known of the physiological and pharmacological actions of *P. ginseng* and ginsenosides in these neurological disorders. Future neurological studies involving *P. ginseng* and ginsenosides should include the therapeutic studies in both animal and human models for these diseases.

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