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Review Article
Anti-aging Effects of Ginseng and Ginsenosides on the Nervous System

[1]Min Lai, [1]Hui-juan Zhang, [1]Fei Wang, [1]Ya-lan Shao, [2]Mei-wen Yang, [3]Fen-fang Hong and [1]Shu-long Yang

[1]Department of Physiology, College of Medicine, Nanchang University, 330006 Nanchang, China
[2]Department of Nurse, The Affiliated Hospital of Jiangxi Academy of Medical Science, Nanchang, 330006 Jiangxi, China
[3]Department of Experimental Teaching Center, Nanchang University, 330031 Nanchang, China

First, Second, Third and Forth Author contributed equally to this work

Abstract

Senescence is the comprehensive manifestation of human body deterioration induced by various environmental factors. Ginsenosides are the main anti-aging ingredients of ginseng. Ginsenoside Rg1 protects the nervous system from aging by promoting human intelligence, inhibiting the release of LDH and MDA and decreasing intracellular calcium overload. Loss of memory and learning ability resulting from aging can be resisted by ginsenoside Rg1, Rb1 and Rg2. Ginsenoside are effective in inhibiting neuronal cell apoptosis and promoting proliferation of these cells. These molecules also inhibit the aging process regulated by the Rb and p53-dependent pathways and exert their function against Alzheimer's disease. In addition, experimental results from animals demonstrated that ginseng saponins protected the brain cortex and regulated TrkB mRNA expression in the hippocampus. This paper reviewed all recent developments in the study of the anti-aging effects of ginseng and its ginsenosides on neural systems to provide a theoretical basis for the clinical application of these molecules in the prophylaxis and treatment of diseases related to the neural system aging.

Key words: Ginseng, ginsenoside, anti-aging, neural system aging, nervous system

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Corresponding Author: Shu-long Yang, Department of Physiology, College of Medicine, Nanchang University, 330006 Nanchang, China
Tel: (+86)13576291532 Fax: (+86)-791-86360556
Fen-fang Hong, Department of Experimental Teaching Center, Nanchang University, 330031 Nanchang, China Tel: (+86)18970965319

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INTRODUCTION

Ginseng is the dry root of the Araliaceae plant and its main effective component is ginsenoside[1]. Ginsenoside is a major pharmacologically active component extracted from the roots, stems and leaves of *P. ginseng* that can improve human immunity and has antifatigue and anti-aging effects. More than 30 kinds of ginseng saponins have been analyzed, the majority of which is Rh and Rg groups, which have contrasting effect on the central nervous system. Rh inhibiting while Rg exciting the system's function. Aging is a comprehensive process resulting from various physical and biochemical reactions. This development is also the interactive result of many factors *in vivo* and *in vitro*. Aging induces numerous changes in the human body, such as the impairment of memory related to the changes in monoamine oxidase B (monoamine oxidase-B) in the brain. Moreover, the body's metabolism and Na-K-ATPase activity in the brain, kidney and myocardial cell membrane are also reduced. Aging-related diseases in the nervous system mainly include mild cognitive impairment and aging degenerative diseases, such as Alzheimer's disease (AD), cataract, glaucoma and Parkinson's disease. AD is an irreversible and progressive brain disease with severe disorder in memory, thinking and behavior[2]. With its unique pharmacological value, ginseng has widely been applied in traditional Chinese medicine clinic for 2000 years. Many years studies have indicated that ginseng and ginsenosides have obvious anti-aging effects and its anti-aging function has a potential role in promoting to reveal the mechanism of human aging[3,4]. At present, great progress has been made in the research on the anti-aging mechanism of ginseng and ginsenosides in nervous system[5-8] but there are still some limitations in these studies such as the signal transduction pathway, the DNA damage repair pathways, the telomerase activity, etc. Therefore, summarized the new progress of anti-aging of ginseng and ginsenosides in recent years. It is of great significance to the development and application of natural anti-aging drugs.

Protective effect and mechanism of ginseng on the aging nervous system: Ginsenoside Rg1 is the key component of ginseng with nootropic and anti-aging effects and enhances basal synaptic transmission. This substance can exert anti-aging function in the brain by upregulating TrkB mRNA expression in the normal bone marrow, promoting the release of neurotransmitter, increasing the content of the neurotransmitter acetylcholine (ACh) and preventing excess nitrate production in the neurons[9].

Ginsenosides Rd and Re (10 μM) strongly reduces cell loss and degeneration and significantly protected process lengths and numbers of neurites in TH+cells. Treatment with ginsenosides inhibits oxidative stress and inflammation. Therefore, the neuroprotective effects of ginsenosides at least partially depend on lowering oxidative stress and anti-inflammation activity[7].

Rg1 inhibited LDH release and DNA fragmentation and reduced human nerve neuroblastoma cells (SHSY5Y) apoptosis induced by1-methyl-4-phenyl-pyridine ion (MPP)[4]. This phenomenon may be related to the ability of Rg1 to eliminate the intracellular reactive oxygen species (ROS). In addition, Rg1-induced delay in the aging process of D-galactose(D-gal)-treated mice may contribute to the enhanced the antioxidation of the brain tissue as well as the downregulation of the mRNA and protein expression of p16 and p21 in the brain tissue.

Shi *et al.*[10] established subacute aging mice model to observe the effects of ginsenosides on some relative enzyme activities in the brain tissue of D-gal-induced aging mice. The results showed that ginsenosides could significantly decrease MDA level but remarkably increase the levels of cerebral super oxide dismutase (SOD) and Na-K-ATP enzyme. Moreover, the MAO-B enzymatic activity was significantly decreased, whereas NOS activity and nitric oxide (NO) levels were considerably increased. These findings suggested that ginsenosides could enhance the antioxidant function and energy metabolism of brain tissues in D-gal-induced aging mice. Moreover, these molecules can improve the peroxidation-produced pathological damage of the brain tissue and reverse the metabolic disorders of neurotransmitter. These processes protect the brain tissue and postpone the aging of the brain (Table 1).

Moreover, He *et al.*[11] evaluated the intracellular calcium ion concentration, cell viability and cell apoptosis index after using different concentrations of ginseng in the hippocampus nerve cells. The results indicated found that Rg1 can prevent ischemia reperfusion induced by intracellular Ca2+overload and protect the hippocampus nerve cells. This process suggests that Rg1 may be applied to the treatment of cerebral ischemia injury. The molecular mechanisms of the effects of ginseng on the brain were found to include glutamatergic transmission, monoamine transmission, estrogen signaling, nitric oxide (NO) production, the Keap1/Nrf2 adaptive cellular stress pathway, neuronal survival, apoptosis, neural stem cell (NSC) and neuroregeneration, microglia, astrocytes, oligodendrocytes and cerebral micro vessels[12].

Table 1: Anti-aging effects and mechanism of Ginseng and Ginsenosides on nervous system

Effects	Pretreatments	Animals	Site of actions	Possible mechanism	References
The decline of learning and memory↓	D-galactose-induced, ginsenoside	Aging mice	Brain tissue	↓MDA,↑SOD, ↓Na-K-ATP enzyme	Shi *et al.*[10]
	Different concentration of ginseng		Nerve cells of hippocampus	↑Ca2 overload Preventing ischemia reperfusion	He *et al.*[11]
	HBG	Mice	The cerebral cortex hippocampus	↑ChAT, VAChT	Lee *et al.*[8]
	Gintonin		Hippocampus	↑CREB, BDNF, LTP	Cha *et al.*[34]
	G-Rg1,G-Rg2	APP/PS1mice	Hippocampus	↑Aβ deposition	Li *et al.*[2]
	Ginsenoside	Aging rats	Brain tissue	↑Ach, ↓AchE activity	Yu *et al.*[15]
	Ginsenoside	Aging rats	Hippocampus	↓Oxidative stress ↑plasticity-related proteins	Yu *et al.*[17]
	Ginsenoside Rg1	Mice	Hippocampus	↑Synapses of pyramidal cells in CA3 area	Salim *et al.*[51]
	PNS Rg1	Aging rats	Hippocampus	↑GR,↑T-SOD, ↓caspase-3 precursor protein	Wang *et al.*[19]
	Ginsenoside Rg2	Mice	Hippocampus	↑Bcl-2,p53 expression↓Bax,hsp70 expression	Zhuang *et al.*[21]
	Ginsenoside Rg1	Aged rats	Hippocampus	↓C-fos mRNA&protein expression	Liu [22]
				↑cAMP/cGMP	
				↓cAMP-PDE activity	
↓Neuronal apoptosis	Ginsenoside Rb2		Neurons	↑SOD, CAT expression	Liu *et al.*[28]
	Ginsenoside Rg1	Rats	Nerve cells	↑Bcl-2,↓Bax,↓caspase-3	
				↑Bcl-2/Bax	Bao *et al.*[9]
	D-gal		Brain	Nrf2 and SIRT1-mediated anti-oxidant signal pathway	Bao *et al.*[26]
	KBG			↑Bcl-2,↓P-P53,Caspase-3	Nguyen *et al.*[5]
	PNS	Rats	Neurons	↓Calmodulin expression	Yang *et al.*[30]
	PNS	Rats	Neurons	↓NO synthesis ↓NO neurotoxicity ↓Oxygen free radical	Zhang and Steiner[31]
Nerve cell proliferation	Intraperitoneal injection of ginsenosides Rg1	Adult rats with	Nerve	↑NSC	Cui *et al.*[54]
		focal cerebral ischemia		↑Nestin expession	Cui *et al.*[36]
				↑Hippocampal cell	Shen and Zhang[38]
Anti-AD	Ginsenoside Rg1	Rats		↑ADAM9, ADAM10, ↓Aβ42	Quirion [55]
	PNS	SAMP8	Brain	↓APP↓Aβ	Zhong *et al.*[41]
	G-Rg1,G-Rg2		Brain	↓The concentration of hypoxanthine,	Li *et al.*[2]
↓Rb and p53 dependent pathways	D-galactose, Ginsenoside Rg1	Aging rats	Brain	↓p16ink4a,p21Cip1 /Waf1 mRNA&protein expression	Peng *et al.*[4]
↓Free radical	Decapitation Ginsenoside 25 (mg kg^{-1}/day)-1	Decapitated rats	basal forebrain, hippocampal formation and cerebral cortex	↓NO, MDA ↑SOD activity	Li *et al.*[45]
↑TrkB mRNA expression	Ginsenoside Rb1	Aged rats	Septum nucleus basal forebrain	↑mRNA expression	Salim *et al.*[51]
	Ginsenoside Rg1		Hippocampus	↑TrkA mRNA	
				↑c-fos mRNA and fos protein expression	
	Ginsenoside Rg1		CA1	↑The dendritic apical spine	
				↑p-AKT, BDNF, proBDNF, glutamate receptor 1	Zhu *et al.*[50]
	Ginsenoside	Aged rats	Hippocampal CA3 and dentate gyrus	↑TrkA mRNA	Lai *et al.*[49]

MDA: Malondialdehyde, SOD: Superoxide dismutase, Ca2: Carbonic anhydrase II, PNS: Panax notoginseng triterpenes, GR: Glutathione reductase, T-SOD: Total superoxide dismutase, Ach: Acetylcholine, AchE: Acetylcholinesterase, cAMP: Cyclic adenosine monophosphate, cGMP: Cyclic guanosine monophosphate, NO: Nitric oxide, ROS: Reactive oxygen species, NSC: Neural stem cells, AD: Alzheimer's disease, Aβ: β-Amyloid peptide, SMAP8: Senescence accelerated mouse-prone 8, APP: Amyloid precursor protein, ChAT: Choline acetyltransferase, VAChT: Vesicular acetylcholine transporter, HRG: High dose red ginseng extract, HBG: High dose black ginseng extract, APP: Amyloid precursor protein, MAPK: Mitogen-activated protein kinase, JNK: Jun amino-terminal kinases, LTP: Long-term potentiation, Aβ: β-Amyloid peptide, Nrf2: Nuclear factor erythroid 2-related factor 2, SIRT1: Silent mating type information regulation 2 homologue

Ginseng suppression of aging-caused decline of learning and memory: Decline in learning and memory is one of the main characteristics of aging. Many mechanisms underlie the learning and memory regulation, one of which is the decreased central cholinergic nerve function which can cause learning and memory disorders[13]. Cheng *et al.*[3] found that the human brain with less Ach usually accompanies learning and memory impairments. Early experiments have shown that Rg1 and Rb1 increased Ach content of the central nervous system, suggesting that the functions of Rg1 and Rb1 may be related to increasing choline acetyltransferase (ChAT) but inhibiting acetylcholinesterase (AchE) activity. Wang *et al.*[14] further confirmed these results because Ach hydrolase and AchE activity may respond to Ach content in the brain. Yu *et al.*[15] performed experiments that confirmed a significant difference between the ginsenoside group and subacute aging model in the escape latency of rats. The AchE activity in the ginsenoside Group was weaker than that in the model group and the content of Ach in brain of the rats in the ginsenoside group increased. These conditions improved the learning and memory abilities of the rats. The study showed that ChAT and vesicular acetylcholine transporter (VAChT) protein levels were significantly increased in all ginseng-treated groups. In addition, significant increase by approximately two-fold in ChAT protein levels was observed in the cerebral cortex of the HBG-treated mice and in the hippocampus of the HRG-treated mice. At all dose levels, the expression of VAChT in the BG-treated groups was up regulated by more than two-fold in the cortex and hippocampus. These results suggested that supplementation with the tested ginseng extracts may suppress the cognitive decline associated with aging via regulation of the cholinergic and antioxidant defense systems[8].

The hippocampus is particularly important for learning and memory. McGaugh[16] found that β-adrenergic receptors are involved in the formation of hippocampal long-term potentiation (LTP), which is commonly considered to be the cellular mechanism of learning and memory. Therefore, the findings showed that ginseng up regulation of the β-adrenergic receptor in the hippocampus maybe one of the mechanisms of its anti-aging and nootropic functions. The study found that oral administration of gintonin for 1 week upregulated the expression of learning- and memory-related proteins, such as phosphorylated cyclic adenosine monophosphate-response element binding protein and brain-derived neurotrophic factor (BDNF). In addition, prolonged gintonin administration enhanced long-term potentiation in the hippocampus[6]. Zhao *et al.*[17] found that ginsenoside reduced oxidative stress, increased plasticity-related proteins in the hippocampus of aging rats and then prevented the memory from decline in these aging rats. Using an evasion reaction test, Ying *et al.*[18] observed that Rg1 can enhance the learning and memory of mice by increasing the number of synapses of pyramidal cells in the CA3 area of hippocampal. In addition, Wang *et al.*[19] found that *Panax notoginseng* saponin (PNS) Rg1 increased the content of glutathione reductase and total superoxide dismutase (T-SOD) in the hippocampus of aging rats, inhibited the activation of apoptosis-related protein cysteine aspartate (caspase-3) precursor protein and improved learning and memory. All these effects are against the aging of rat nervous system. Furthermore, Rg1 can resist cognitive impairment resulting from chronic irritability, which may be related to the ability of Rg1 to regulate the calcium concentration in the hippocampal cells, inhibit several hippocampal neuron necrosis or apoptosis and protect the hippocampal formation from damage[20].

β-Amyloid peptide (Aβ) can lead to synaptic dysfunction that is a major pathogenesis of cognitive impairment. Cytotoxic effect of Aβ deposition can induce neuronal apoptosis. Bcl-2 is inhibitory but Bax is a stimulative neuronal apoptosis protein gene. These genes constitute a pair of balanced system. Zhuang *et al.*[21] found that Aβ decreased Bcl-2 but increased Bax expression in the hippocampus of mice, thereby inducing neuronal apoptosis. Ginsenoside Rg2 upregulated the expression of Bcl-2 and P53 but downregulated the expression of Bax and HSP70 in the hippocampus of mice. This result indicated that Rg2 may regulate the expression of apoptosis protein and inhibit neuronal apoptosis induced by Aβ deposition, thus protecting the learning and memory functions of mice. By contrast, marked morphological changes have been observed in the mouse AD model. Neurons were loosely organized and darkly stained and dark brown and scattered Ab deposits were observed. The pathological abnormalities observed in APP/PS1 mice were gradually ameliorated after G-Rg1 and G-Rg2 treatment. Clear nucleoli and light brown, sparsely scattered Ab deposits were visible. Thus, G-Rg1 and G-Rg2 partially enhanced impaired cognitive function and increased hippocampal Aβ deposition in the APP/PS1 mice[2].

Accumulated evidence has shown that c-fos gene expression and its protein biosynthesis are essential for learning and memory of animal or human beings. Liu *et al.*[22]found that Rg1 could significantly upregulate the expression of c-fos mRNA and protein in the hippocampus of aged rats. Moreover, this molecule also selectively increased the content of cyclic adenosine monophosphate (cAMP) in the tissue. Thus, cAMP/cGMP ratio was increased accordingly. At the

same time, Rg1 significantly inhibited the activity of cAMP-dependent phosphodiesterase (cAMP-PDE) elevated the intracellular cAMP levels and promoted the c-fos gene expression. These results suggested that Rg1 reduced cAMP hydrolysis by inhibiting cAMP-PDE activity and this reduction led to elevated cAMP levels and increased c-fos gene expressions and its protein biosynthesis to present nootropic activities[20].

Ginseng inhibition of neuronal apoptosis: Apoptosis and its related factors in AD have been widely investigated since Lassmann and Samal showed nerve cell apoptosis in AD brain by autopsy[23,24]. Chen et al. reported that Rg1 inhibited MPP+induced-SHSY5Y cells apoptosis and its underlying mechanism may be by eliminating ROS, decreasing c-jun- N-terminal kinase (JNK) activity and preventing caspase-3 activation[20]. Oxidative stress is shown to be directly involved in the pathogenesis of AD and other neurodegenerative diseases. This condition breaks the dynamic balance of anti-oxidation and oxidative states in the body, accelerates the aging of the central nervous system and induces cell apoptosis in the nervous system[25]. Saponins from *Panax japonicus* (SPJ) remarkably decreased lipofuscin levels, increased hippocampus nuclear factor erythroid 2-related factor 2 (Nrf2) and silent mating type information regulation 2 homologue (SIRT1) protein levels and anti-oxidant genes expression, such as manganese SOD, hemeoxygenase, NAD(P)H quinone oxidoreductase 1 and cysteine ligase catalytic in D-gal-induced brain aging. D-gal induced multiple molecular and functional changes in the brain similar to the natural aging process. SPJ protected the brain from D-gal-induced neuronal injury by decreasing oxidative stress and apoptosis and ultimately improving cognitive performance. This process is possibly related to Nrf2- and SIRT1-mediated anti-oxidant signaling pathways[26]. Wang *et al.*[19] showed that PNS Rg1 can improve the content of GR and T-SOD against oxidative stress, inhibit the activation of caspase-3 cleavage of the precursor protein and prevent apoptosis and aging of the nervous system. Ying *et al.*[18] discovered that purified ginsenosides Rg1 can reproduce adult NSCs and then differentiate these cells into neurons. The mitochondrial membrane protein Bcl-2 can prevent the release of Cytochrome-Cto inhibit neuronapoptosis, decrease peroxide production and improve the survival rate of neurons[27]. Chang *et al.*[28] reported that panoxadiol, especially ginsenoside Rb2, induced the gene expression of SOD and catalase in the neurons by 2-3 times of the total saponins. SOD can catalyze the conversion of superoxide radicals to hydrogen peroxide and molecular oxygen and then inhibit neuronal apoptosis.

Bao *et al.*[29] also confirmed that ginsenoside Rg1 can suppress the ischemia reperfusion-induced cell apoptosis in rats by regulating its multiple gene protein expression. Rg1 upregulated Bcl-2 protein expression, downregulated the protein expression of Bax and caspase-3 and increased the Bcl-2/Bax ratio to reduce cell apoptosis. In addition, Rg1 also down regulated the gene expression of FAS and FAS-Land intervened in the JNK signaling pathway to inhibit neuronal apoptosis[11]. KRG-treatment upregulated BCL2 expression and downregulated expression of p-p53 and caspase-3,indicating that KRG protects against apoptosis induced by oxidative stress[5].

Yang *et al.*[30] reported that PNS down regulated calmodulin expression of the nerve by suppressing Ca^{2+} influx. This substance also inhibited NO synthesis, reduced NO neurotoxicity and oxygen free radicals and alleviated mitochondrial damage to increase the energy synthesis[31]. Furthermore, the decrease in calmodulin B in the nerve prevented changes in the chromosome structure and avoided neuronal apoptosis caused by endonuclease activation-induced DA fragmentation[32]. PNS also inhibited the mitogen-activated protein kinase kinase 4 (MAPKK4), then weakened nerve cell differentiation and death by MAPK signal pathway and inhibited brain aging[33].

Ginseng promotion of nerve cell proliferation: Transplantation of stem cells into the brain attenuates functional deficits in the central nervous system by cell replacement, release of specific neurotransmitters and production of neurotrophicfactors[34]. Treatment with ginseng total saponins (GTS) (5-80 mg kg^{-1}) after a TBI improved the recovery of neurological functions, including learning and memory and reduced cell loss in the hippocampal area. GTS treatment (20 mg kg^{-1}) after a TBI upregulated the expression of NGF, GDNF and NCAM, inhibited the expression of Nogo-A, Nogo-B and TN-C and increased the number of BrdU/nestin positive NSCs in the hippocampal formation. GTS regulated the expression of nerve growth-related factors and improved the proliferation of neural stem/progenitor cells. These phenomena might facilitate neural regeneration and tissue repair and contribute to the recovery of neurological functions, including learning and memory[35]. In addition, Cui *et al.*[36] showed that Rg1 can promote proliferation and differentiation on the focal cerebral ischemia in rat NSCs. Intraperitoneal injection of Rg1 can significantly increase the number of NSC in the brain ischemia in adult rats. This event suggests that Rg1 can promote nerve regeneration, with the ability to promote the proliferation of NSCs. They also confirmed that Rg1 is beneficial in maintaining cell viability

and promoting growth of nerve cell projections, which has been regarded as basic fibroblast growth factor in a similar role with the promotion of cerebral ischemia after NSC proliferation[29]. In addition, they also found that Rg1 could promote ischemic brain region nestin (Nestin) expression after cerebral ischemia[36]. Nestin-positive cells can differentiate into mature neurons and glial cells, replacing lost cerebralneurons during ischemia[36]. Intraperitoneal injection of Rg1 leads to the enhanced differentiation of adult hippocampal cell number, suggesting that Rg1 may be related to the hippocampal precursor cell proliferation, which may also be one of the neuroprotective and anti-aging mechanisms[37,38].

Anti-AD effect of ginseng: The molecular mechanisms of the neuroprotective effects of ginseng in AD against β-amyloid (Aβ) formation, tau hyperphosphorylation and oxidative stress, major depression, stroke, Parkinson's disease and multiple sclerosis have been demonstrated [12]. Unusual increase in Aβ has been confirmed as the key factor leading to the occurrence and development of AD. The deposition of Aβ damages the cholinergic nerve cell, leading to decreased levels of ChAT and Ach neurotransmitter synthesis. Liu *et al.*[39] found that Rg1 increased the amyloid precursor protein (APP) metabolic pathway á-secretase ADAM9 and ADAM10 gene expression and enhanced á-secretase metabolic pathway of APP. These processes indirectly reduced the production of Aβ42. Shao *et al.*[40] found that Rg1 could cut APP gene expression, increase neural endopeptidase (neutral endopeptidase, NEP) expression, regulate NEP activity and reduce generated Aβ. Zhong *et al.*[41] found that PNS has an effect in the treatment for the accelerated dementia mouse SAMP8 brain model through inhabiting the deposition of $A\beta_{1-40}$ and $A\beta_{1-42}$ and reduing the content of App,which itself is achieved by downregulating the expression of the App gene. Abnormal brain hypoxanthine concentration could be one of the factors leading to AD and G-Rg1 and G-Rg2 may improve the metabolism of hypoxanthine and decrease the concentration of hypoxanthine, which is associated with AChE and oxidative stress. These phenomena alleviate symptoms of AD[2]. Another study have also shown that Rg1 could inhibit glycogen synthase kinase 3β (GSK-3β) activity and decrease phosphorylation of tau protein[42].

Ginseng anti-Rb and p53-dependent pathways regulating aging: The p16 and p21 genes were the two key regulatory factors in the Rb and p53-dependent regulation of senescence-induced pathway[43]. Numerous studies had shown that high expression of p16 and p21 could induce cell senescence[38]. Peng *et al.*[4] demonstrated that Rg1 can cut the mRNA and protein expression of D-gal- aging rats brain p16ink4a and p21Cip1/Waf1, preventing the cells within the brain tissue into the aging program and postponing the aging of the brain.

Ginseng anti-free radical protection in aging rat basal forebrain cortex: The basal forebrain, hippocampus and cerebral cortex are important parts of the learning and memory loop. Many scholars believe that increase in the free radical content is an important cause of body aging and aging-related diseases[44]. High levels of free radicals in the body cells can cause oxidation of unsaturated fatty acid peroxide, resulting in the damage of cell membranes, intracellular macromolecules substanceproteins, DNA and enzymes as well as accelerated cell aging and death. In addition, various enzymes remove free radicals but these enzymes decreases with increasing age. The NO and MDA contents as well as SOD activity, of aged rats directly affected cognitive function in the basal forebrain cortex system. Thus, measuring the NO and MDA contents in the aged rats can reflect the extent of brain aging. By contrast, SOD activity measured from the molecular mechanisms of cerebral protection levels reflect the functional status[45]. Li *et al.*[45] found that the NO, MDA content in basal forebrain, hippocampal formation and cerebral cortex of the 27-month rats are higher than those in the young group and SOD activity decreases with increasing age. Pellmar *et al.*[46] reported a radical by interfering with the second messenger involved in LTP and accelerating the destruction of hippocampal CA1 LTP. Harris *et al.*[47] reported that free radical damage to cell membranes of neurons and intermediate products were associated with Aβ induction. This result suggested that free radicals on the basal forebrain, hippocampal formation and oxidative damage to the cerebral cortex may be the key factors of the aging of animal brain and cognitive impairment key factor. Rg1 is an important component of ginseng, which can reduce ischemic injury of the cerebral cortex, significantly reduce MDA production and significantly increase SOD activity[48]. Li *et al.*[45] gave decapitated rats ginsenoside 25 (mg kg^{-1}/day)-1 dose and found that the NO, MDA content in basal forebrain, hippocampal formation and cerebral cortex decreased. The SOD activity in the treatment group is significantly higher than the aged group. These findings displayed that ginsenoside had anti-aging effects and its mechanism may be involved in the aging brain against free radicals and SOD-like action.

Ginseng promotion of TrkB mRNA expression in the hippocampus of aged rats: Lai *et al.*[49] showed that aging can the change level of the TrkB mRNA expression level during the hippocampal neuron formation. Aged rats with BDNF and other antiporter obstacles and decreased hippocampal formation may be the main factors of neuronal atrophy, malnutrition and decrease in receptor TrkB mRNA. These phenomena eventually become the important reasons for the loss of cholinergic neurotransmitters and reduced cognitive aging. Rg1 administration increased the dendritic apical spine numbers and area in the CA1 region. In addition, Rg1 administration up regulated the expression of the hippocampal p-AKT, BDNF, proBDNF and glutamate receptor 1.These data suggested that Rg1 treatment improves memory in middle-aged mice possibly by regulating the PI3K/AKT pathway, altering apical spines and facilitating hippocampal LTP[50]. Studies have demonstrated that Rb1 promoted the hippocampus and septum nucleus of nerve growth factor (NGF) before mRNA expression and the basal forebrain TrkA mRNA. Rg1 enhanced the hippocampus of the neuronal apoptosis gene c-fos mRNA and fos protein expression in aged rats[51], while Rb1 and Rg1 showed protection and nutrition effects on neurons, promote neuronal regeneration, enhance the ability of neuronal injury and apoptosis resistance and improve learning and memory. Rb1 has special effects on memory acquisition and representation, improving the structure of the aging rat hippocampal neurons of the neurotransmitter[52]. Lai *et al.*[49] observed that the TrkB mRNA expression in the aging structure of rat hippocampus neurons in three sub-regions was significantly reduced. The structure of the hippocampus neuronal morphology neurotrophic factor and its receptor in a disability caused by functional changes may be associated with cognitive decline in older animals. By contrast, the expression of GS-administered group hippocampal CA3 and dentate gyrus neurons TrkB mRNA was significantly increased. These results suggest that ginsenoside may improve learning and memory in aged rats as an important regulatory function[49].

Other anti-aging effects of ginseng: Studies had shown that synaptophysin (SYP) mRNA content decreased during the aging process. Lv *et al.*[53] found that PNS can increase the content of SYP mRNA, suggesting that one of the mechanism of its anti-aging effect may be the upregulation of SYP gene expression induced by PNS. Yang *et al.*[30] found that voltage-gated sodium channel 2B subunit (sodium channel voltage gated type II B, SCN2B) gene expression was significantly upregulated in Hippocampus japonicus when adult mice were treated with PNS. This phenomenon may be related to the enhancement of the sodium ion channel function, maintenance of impulse formation and conduction of nerves, strengthening of the connections between neurons, protection of the neurons, promotion of the repair of nerve cells and certain preventive effect on brain aging.

CONCLUSION

In conclusion, Rg1 exhibits a good anti-aging effect on the nervous system, which was reflected in the prohibition of learning and memory decay resulted from aging, inhibition of the apoptosis of nerve cells and promotion of the proliferation of the nerve cells. Furthermore, Rg1 can resist AD, among others. These results presented great value in the development and utilization of ginseng and ginsenoside to prevent and treat of nervous system-related diseases. More in-depth investigation of the mechanism of the effects of Rg1 on the anti-aging function in the nervous system is needed to provide an experimental foundation for the clinical application of ginseng and saponins in the treatment of diseases, such as AD. These studies are remarkably beneficial for the old adult population. Recent studies have highlighted the potential use of ginseng in the prevention and treatment of chronic inflammatory diseases, such as diabetes, rheumatoid arthritis, cancer, depression and allergic asthma. Several herbal ingredients containing ginseng have been used in the treatment of cancer radiotherapy and chemotherapy. When used in combination with chemical agents, these substances reduce the amount of chemical used and side effects during treatments. Rg1 may be used as a therapeutic agent for cerebral ischemic injury. Ginseng can delay brain aging.

SIGNIFICANT STATEMENT

This study discovered that Ginsenoside Rg1 protects the nervous system from aging by promoting human intelligence, inhibiting the release of LDH and MDA and decreasing intracellular calcium overload. Ginsenoside can inhibit neuronal cell apoptosis and promote its proliferation too. Moreover, ginseng saponins protected the brain cortex and regulated TrkB mRNA expression in the hippocampus. Loss of memory and learning ability resulting from aging can be also resisted by ginsenoside Rg1, Rb1 and Rg2. Thus, the anti-aging effects of ginseng and its ginsenosides on neural systems provide a theoretical basis for the clinical application of these molecules in the prophylaxis and treatment of diseases related to the neural system aging.

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