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A comprehensive review of the therapeutic and pharmacological effects of ginseng and ginsenosides in central nervous system

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Ginseng is one of the most widely used herbal medicines in human. Central nervous system (CNS) diseases are most widely investigated diseases among all others in respect to the ginseng's therapeutic effects. These include Alzheimer's disease, Parkinson's disease, cerebral ischemia, depression, and many other neurological disorders including neurodevelopmental disorders. Not only the various types of diseases but also the diverse array of target pathways or molecules ginseng exerts its effect on. These range, for example, from neuroprotection to the regulation of synaptic plasticity and from regulation of neuroinflammatory processes to the regulation of neurotransmitter release, too many to mention. In general, ginseng and even a single compound of ginsenoside produce its effects on multiple sites of action, which make it an ideal candidate to develop multi-target drugs. This is most important in CNS diseases where multiple of etiological and pathological targets working together to regulate the final pathophysiology of diseases. In this review, we tried to provide comprehensive information on the pharmacological and therapeutic effects of ginseng and ginsenosides on neurodegenerative and other neurological diseases. Side by side comparison of the therapeutic effects in various neurological disorders may widen our understanding of the therapeutic potential of ginseng in CNS diseases and the possibility to develop not only symptomatic drugs but also disease modifying reagents based on ginseng.

Keywords: *Panax ginseng*, Alzheimer's disease, Parkinson's disease, Ischemia, Neurodevelopmental disorders

INTRODUCTION

Ginseng is any one of the perennial plants, which are included in genus *Panax* and family *Aralliaceae*. Among eleven different species of ginseng commonly called as ginseng, three species of ginseng, i.e., *Panax ginseng* (commonly called as ginseng or Korean ginseng), *P. quinquefolius* (commonly called as American ginseng) and *P. notoginseng* (commonly called as Chinese no-toginseng or Sanchi) are the three most commonly used ginseng herbs at present [1]. Ginsenoside is believed to be the active compounds of ginseng herbs and widely used for the pharmacological examination of effects of ginseng ranging from the role as a traditional nourish-ing stimulant to anticancer reagent. Ginsenosides are classified into three categories based on their structural differences. The panaxadiol group includes Rb1, Rb2, Rb3, Rc, Rd, Rg3, Rh2, and Rs1 and panaxatriol group includes Re, Rf, Rg1, Rg2, and Rh1. Ro is classified as oleanolic acid group [2]. The investigation on the beneficial and sometimes harmful effects of ginseng in various pathological conditions keeps growing to previously unexpected extents and for example, it has been suggested that the combination of red ginseng with highly active anti-viral therapy may improve the clinical outcome of human immunodeficiency virus type 1-infected patients

[3]. Growing number of publications are also attributed to the effects of ginseng and ginsenosides on central nervous system (CNS) disorders. These disorders in CNS are not only confined to the traditional target diseases such as stress and ischemia but also expand into more recently acknowledged neurological and psychiatric disorders including Alzheimer's disease (AD) and attention deficit hyperactivity disorder (ADHD).

Recently, several reviews are published about the role of ginseng or ginsenosides on neurological functions or possible target proteins including different types of ion channels. For example, ginseng or ginsenoside affects neurotransmission of acetyl choline and gamma-aminobutyric acid (GABA) by mechanism involving the regulation of the expression of synthetic enzyme, neurotransmitter release as well as the signaling pathways involved in the particular neurotransmitter systems. Ginseng and ginsenosides improve learning and memory as determined by behavioral analysis by mechanism involving alteration of synaptic plasticity and increase in neurogenesis, thereby affecting neuronal density in hippocampus. Ginsenosides affect voltage and ligand-gated ion channels including K^+, Na^+, and Ca^{2+} channels as well as N-methyl-D-aspartate (NMDA)-, nicotine-, and serotonin-gated ion channels (for a review, see [4]). Recently, growing expectations about the role of ginseng and ginsenosides in the regulation of stem cell proliferation and differentiation as well as the more comprehensive understanding of classical neurotrophic role of ginseng may confer enthusiasm in investigating the role of ginseng in CNS disorders such as stroke, AD, Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD). At the moment, the most extensively studied effects of ginseng and related compounds are their effects on stroke and AD. In addition to the descriptive studies depicting the efficacy of ginseng and ginsenosides in animal models of disease as well as their neuroprotective role in terms of anti-oxidant, anti-inflammatory, and anti-apoptotic activity, more specific cellular and molecular mechanisms are now revealed, which dictates close overviews on the role of ginseng and ginsenosides in CNS disorders. However, extensive reviews on the role of ginseng on the neurological and psychiatric diseases are scarce not to mention the mechanism of ginseng mediating the regulatory role in those diseases. In this review, we will summarize the works conducted regarding the effects of ginseng (the three conventional ginseng species excluding Siberian or Indian ginseng) and ginsenosides in various CNS diseases using cell culture and animal models as well as human clinical studies in an hope to systematically understand the effects and mechanism of ginseng in CNS disorders.

ALZHEIMER'S DISEASE

With the in-depth understanding of molecular and cellular pathophysiology and neurobiology of AD during last couple of decades, many plausible targets to treat AD have been suggested which include but not restricted to followings: 1) increase in the uptake of choline in central nervous system, 2) release of acetylcholine from hippocampus, 3) increased activity or expression of choline acetyltransferase, 4) protection against the Aβ or tau protein-induced neurotoxic effects by several mechanisms including inhibition of neuroinflammation, increased production of neurotrophic factor, and regulation of apoptotic processes, 5) repair of Aβ-damaged neuronal networks by increased neurogenesis and synaptic plasticity, and 6) reducing the level of Aβ by decreased production or increased elimination. Actually, many of these pathophyiological targets and the effects of ginseng and ginsenosides on them are subjected to the intense investigation and covered by several recent reviews [5,6].

Regulation of neurite outgrowth and synaptic plasticity by ginseng

Based on the fact that protopanaxadiol-type saponins were active constituents mediating neurite outgrowth in human neuroblastoma SK-N-SH [7], it has been demonstrated that ginsenoside Rb1 and its intestinal metabolic compounds M1 recovered the impaired spatial memory and expression levels of phosphorylated NF-H and synaptophysin in an animal model of AD induced by intracerebroventricular injection of Aβ(25-35) [8]. In cultured cortical neurons, M1 increased axonal outgrowth even after substiantial progress of neurite degeneration, suggesting a neuro-regenerative potential of this compound. Similar neurite outgrowth potential of crude ginseng saponin was also reported in cultured rat cerebral cortical neurons [9]. In addition, ginsenoside Rb1 potentiated the nerve growth factor (NGF)-mediated neurite outgrowth of cultured chick embryonic dorsal root ganglia [10]. Interestingly, the memory impairment induced by intracerebroventricular injection of Aβ(25-35) as well as synaptic marker protein expression is only marginally increased by donepezil, if any, consistent with its primary mechanism of action, i.e., the inhibition of acetylcholine esterase [8]. In addition, the memory improving effects of Rb1 or M1 were maintained even after the discontinuation of Rb1 and M1 administration suggesting they

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induced a long lasting and probably structural reorganization of the damaged brain circuits, which is ideal for the treatment of neurodegenerative conditions including AD although further verification in other animal models of AD is needed in the future. Neurite outgrowth is one of the foremost phenotypical changes in network reorganization, which might be one of the cellular and molecular changes happening during synaptic plasticity, which suggests that the observed neurite extension effects of ginseng may underlie the memory enhancing effects of ginseng in both normal and pathological conditions, although clinical studies produced both positive and negative results (see below).

In the dentate gyrus of anesthetized rats, i.c.v. injection of ginsenoside Rb1 (10, 100 nM) inhibited the induction phase of long term potentiation (LTP) and accelerated the maintenance phase of LTP induced by high frequency stimulation in a dose-dependent manner [11]. In addition, treatment with nonsaponin fraction of ginseng significantly ameliorated deficits in place-navigation learning in the aged rats in the place learning task along with significant augmentation in the increase in population spike amplitudes in the CA3 subfield after LTP induction *in vitro* [12]. Similarly, ginsenoside Rg1 inhibited morphine induced spatial memory deficit which was determined by Morris water maze test and restored LTP impaired by morphine in both freely moving and anaesthetized rats, which was examined by electrophysiological recording after implantation of electrodes *in vivo* [13]. The electrophysiological recording *in vitro* also demonstrated that Rg1 restored the LTP in slices from the rats treated with morphine without affecting LTP in the slices from normal rats. The restoration LTP is inhibited by NMDA receptor antagonist MK801 suggesting the involvement of NMDA receptor activation in the Rg1-induced recovery of LTP [13]. Using acutely isolated rat hippocampal CA3 pyramidal neurons with a conventional whole-cell patch-clamp technique, it has been suggested that Compound K, a metabolite of Rb1, enhances spontaneous GABA release by increasing intraterminal Ca^{2+} concentration via Ca^{2+} release from pre-synaptic Ca^{2+} stores, although how these findings are related to the regulation of hippocampal excitability and learning and memory processes remains to be determined [14].

Morphologically, Rg1 increased chronic mild stress induced decrease in dendritic spine number and hippocampal neurogenesis [15], which also suggests the modulation of processes involved in synaptic plasticity by ginsenosides.

Ginsenoside Rg1 and Rb1increased proliferation and differentiation of neural progenitor cells in dentate gyrus of hippocampus of normal adult mice and global ischemia model in gerbils. In addition, Rg1 increased expression of brain derived neurotrophic factor, Bcl-2 and antioxidant enzyme and increased the number of synapses and mossy fiber sprouting in CA3 regions of hippocampus suggesting the role of Rg1 in the modulation of synaptic plasticity and possibly to the increased cognitive function in AD [16]. Similarly, when the mixture of brain-derived neurotrofic factors (BDNF) and ginsenosides Rg1 and Rb1 was treated to human neural stem cell during the differentiation procedure, it promoted cell survival and enhanced neurite outgrowth and the expression of synaptic marker proteins, which was evidenced by time lapse microscopy, immunostaining, and Western blot [17].

Neuroprotection

Ginsenosides have direct neuroprotective effects against glutamate or Aβ stimulation. In cultured PC12 cells, glutamate decreased cell viability and increased intracellular calcium concentration and lipid peroxidation, which is evidenced by the excessive production of malondialdehyde and nitric oxide (NO) [18], all of which are prevented by ginsenosides. Whether the neuroprotective effects against glutamate has been related with the reported antagonistic activity of many ginsenoside such as Rg3 and Rh2 against NMDA receptors remains to be determined (for a review, see [19]). The antioxidant effects of ginseng has also been implicated in a study showing the neuroprotective effects of ginseng extracts in human neuroblastoma SY-5Y cells [20]. Treatment of SY-5Y cells with cyclosporine A inhibited calcineurin activity, which results in hyperphosphorylation of tau protein. Pretreatment of ginseng extracts effectively enhanced calcineurin activity, which ameliorates tau phosphorylation providing possible neuroprotective activity [20]. Treatment of ginsenoside Rg2 effectively and significantly attenuated the glutamate-induced toxicity and changes in above mentioned factors. In addition, ginsenoside Rg2 decreased the level of glutamate-induced increased protein expression such as calpain II, caspase-3, and Aβ(1-40) in PC12 cells. In addition, treatment of water extracts of American ginseng significantly attenuated the cellular apoptosis of SH5-SY cells induced by Aβ(25-35), which was determined by staining with Hoechst 33258 [21]. Treatment of 50 μM Aβ(25-35) for 48 h also produced cell toxicity in PC12 cells and treatment of ginsenoside Rg1 inhibited β-secretase activity *in vitro* and protected PC12 cells from cell death along with inhibition of NO

release, lipid peroxidation, reactive oxygen species (ROS) production, and elevation of intracellular calcium concentration. Similar neuroprotective action of Rb1 in PC12 cells treated with Aβ(25-35) has been reported by a separate group of researchers [22], which is also related to the increased ratio of anti-apoptotic/apoptotic protein Bcl-2/Bax . Not only neuron but also astrocytes is protected by ginsenosides [23]. In cultured type I rat brain astrocytes (RBA), ginsenoside Rh2 inhibited Aβ-induced inhibition of RBA growth, which is mediated by induction of pituitary adenylate cyclase-activating polypeptide (PACAP) and PACAP receptor PAC1 [24].

Anti-inflammatory effects

Due to the chronic neuroinflammatory responses occurring in AD and other neurodegenerative diseases, researchers investigated the anti-inflammatory effects of ginseng in brain. Several ginsenosides such as Rd, Rg1, Re, Rg3, Rh2, and Rb1 has been suggested to modulate neuroinflammatory responses in cultured microglia or stimulated brain [25-28]. In a mouse model of neuroinflammation induced by intracerebroventricular injection of Aβ(1-42), ginsenoside Rb1 reduced neuroinflammation as detected by cyclooxygenase-2 and inducible nitric oxide synthase (iNOS) expression. Remarkably, 4 wk treatment of Rb1 at the stage of eminent neuroinflammation by Aβ(1-42) (2 wk after treatment), still effectively reduced inflammation along with the improvement of cognitive function as determined by Morris water maze test [29]. The anti-inflammatory effects of Rb1 seem to involve NF-κB pathway as evidenced by the modulation of the level of IκB. More recently, strong anti-inflammatory effects of ginseng saponin metabolite, compound K [20-O-d-glucopyranosyl-20(S)-protopanaxadiol], have also been reported in two different *in vivo* models of neuroinflammation, i.e., sepsis and ischemia [30]. Not only the production of inflammatory mediators but also the recruitment of inflammatory cells into stimulated brain might be modulated by ginseng saponins, which might be regulated by the modulation of expression of intercellular adhesion molecule-1 [31]. In rat model of inflammation, Rg1 stimulated the production of NO and proinflammatory cytokines (interleukin [IL]-1β, IL-6, and tumor necrosis factor [TNF]-α), whereas Rb1 exerted a significant inhibitory effect on the same proinflammatory mediators [32], which might suggest that the regulation of inflammatory response by ginseng and ginsenosides is critically dependent on the relative concentration and kinetics of treatment of individual components of ginseng.

The anti-inflammatory effects might be related to the antioxidant property of ginseng. In a 7 mo chronic treatment experiment, it has been suggested that 100 or 200 mg/kg/d treatment of ginsenosides through drinking water improved memory loss in senescence accelerated mice (SAMP8) along with increase antioxidant levels in serum [33]. The levels of plasticity related proteins including p-CAMKII, pCREB, and BDNF are increased in the hippocampus of ginsenoside-treated mice although it should be determined whether the increased antioxidant activity has causal relationship with the increased expression of plasticity related proteins as well as the improvement of memory in senescence accelerated mice.

Although much of the anti-inflammatory action of ginsenosides is dependent on the modulation of NF-κB activity [26,29], anti-inflammatory activity of some of the ginsenosides such as Rh2 has been reported to be dependent on signaling pathways such as activator protein 1 and protein kinase A (PKA) [28,34] but not by NF-κB [28]. In addition, regulation of inflammatory mediators such as cytokines and NO seems to be regulated by different signaling pathways, for example, mitogen-activated protein kinase and NF-κB pathways in different cell lines [27,35]. These results suggest that the regulation of cellular inflammatory response by ginseng and ginseng saponins is regulated by cell type and particular ginsenoside-specific manners, which necessitates fine dissection of the cellular signaling pathways involved.

Effects on overall Aβ production

Using cell based assay system, which is a Chinese hamster ovary (CHO) cell line stably transfected with human APP 695wt, to detect the accumulation of Aβ, Chen et al. demonstrated that certain ginsenosides lowered Aβ concentration secreted into the culture supernatants in a dose-dependent manner [36]. The strongest effects were observed with ginsenoside Rg3 having an approximate IC_{50} of under 25 μM against Aβ42. Among the various ginsenosides tested to be positive in the reduction of Aβ, ginsenoside Rg1, Rg3, and RE resulted in significant reductions in the amount of Aβ detected in the brains of an animal model of AD, which is Swedish mutant model of familial AD (Tg2576 line), after single oral administration, albeit small in extent compared with a known γ-secretase inhibitor LY411575. Unfortunately, the authors can not provide what would be the actual molecular mechanism of the observed Aβ-lowering effects of ginseng and ginsenosides.

As well as protecting cultured PC12 cells from Aβ-induced toxicity, a flavonol ganglioside isolated from roots of *P. notoginseng* (RNFG) inhibited the aggrega-

tion of Aβ in an *in vitro* assay in a dose-dependent manner [37]. It has been suggested that specific sugar moiety is required for the neuroprotective activity because the flavonol backbone was devoid of neuroprotective activity. No structural similarities to the currently available aggregation inhibitors have been suggested, which gives another level of complexity for the understanding of the possible protective mechanism of RNFG.

Effects on β-secretase activity

The level of β-site APP-cleaving enzyme 1 (BACE1) is responsible for the elevation of Aβ peptides in the brain of AD patients and the expression of BACE1 can be regulated by peroxisome proliferator-activated receptor-γ (PPARγ) by binding to its promoter region. In N2a-APP695 cells, Rg1 decreased the levels of secreted Aβ(1-40) and Aβ(1-42) as well as β-CTFs, a cleaved C-terminal fragment of APP by BACE1. The expression levels of both BACE1 mRNA and protein were decreased in cells treated with Rg1. Rg1 induced activation of PPARγ was demonstrated by the nuclear translocation of PPARγ and Rg1 is suggested to have PPARγ agonist activity like rosiglitazone [38]. In addition, Rb1 inhibited BACE1 activity *in vitro* and rescue PC12 cells from Aβ(25-35)-induced toxicity as determined by LDH release, NO release, ROS production, lipid peroxidation, intracellular calcium elevation, and apoptosis [23]. Interestingly, Rg1 treatment also inhibited activity of γ-secretase in transgenic AD mice over-expressing APP/Aβ (Tg mAPP) as well as B103-APP cells [39]. In addition, Rg1 enhanced activation of PKA/CREB pathway suggesting the multi-target action of Rg1 against AD. In a more recent study using human platelets, it has been demonstrated that Rg1 promoted α-secretase cleavage of APP via estrogen receptor (ER) extranuclear signaling pathway suggesting Rg1 behaves as phytoestrogen, which might have important implications considering estrogen withdrawal as a risk factor for AD [40,41].

Aβ clearance

Although most of the studies dealing with the role of ginseng on glial cells have focused on the anti-inflammatory activity, Joo and Lee [42] focused on the phagocytic role of microglia and found that Rg3, a by-product of red ginseng, enhances the microglial Aβ uptake, internalization, and digestion. The increased clearance of Aβ by microglia by Rg3 seems to be mediated by the increased expression of macrophage scavenger receptor type A, which may provide an additional therapeutic target of AD by ginseng.

In SK-N-SH cells transfected with SweAPP, ginsenoside Rg3 reduced the level of Aβ40 and Aβ42, probably due to the increase in gene expression of neprilysin [43], which has been suggested to be the rate-limiting enzyme in the Aβ degradation in the brain [44]. Whether other proteases such as martix metalloproteinase, angiotensin converting enzyme, and tissue plasminogen activator, which has been implicated in Aβ clearance, were also affected by ginsenoside remains to be investigated. At present, the data investigating whether ginseng and ginsenosides may affects Aβ-clearance through transport across the blood-brain barrier by modulating the regulator molecules such as receptor for advanced glycation end products and lipoprotein receptor-related protein are not available, which may need further investigation.

Effects on tau phosphorylation

Increased phosphorylation of tau protein can results in self aggregation, which is involved in the pathogenesis of AD. After exposure to Aβ(25-35), the levels of tau protein phosphorylation in hippocampal neurons at the sites of Thr205, Ser396, and Ser404 were increased as well as the level of p25. Pretreatment with ginsenoside Rb1, at least in part, reversed these changes [45]. Similarly, Rb1 reduced the phosphorylation of tau induced by Aβ(1-42), which is regulated by a cascade of signaling pathways comprised with PI3K-Akt-GSK3β [46]. Total ginsenosides extracts also partially inhibited cyclosporine-induced increase in tau phosphorylation in SY-5Y cells [20]. Using the slice culture of brain obtained from 5 weeks old Wistar rats, it has also been suggested that ginsenoside Rg1significantly inhibited okadaic acid-induced phophorylation of tau [47]. The same group of researchers also reported that pretreatment of ginsenoside Rd inhibited okadaic acid-induced tau phosphorylation in cultured neuron as well as in brain of male Sprague Dawley rats bilaterally micro-infused with okadaic acid into the cerebral ventricle, which might be mediated by the activation of PP-2A [48].

Effects on cholinergic system

Loss of cholinergic neurons in cerebral cortex and hippocampus is closely associated with AD. Panaxynol, one of the compounds isolated from the lipophilic fraction of *P. notoginseng*, concentration-dependently up-regulated the number of M_1 receptor in CHO cells transfected with human m_1 subtype gene [49]. Panaxynol caused a significant stimulation of cAMP accumulation and the increase in M_1 receptor number was blocked by a PKA inhibitor RP-cAMP. In PC12 cells it has been suggested that Rb1

and Rg1 increased neurotransmitter release by modulating the phosphorylation of synapsin in PKA dependent and independent manner, respectively [50].

Ginsenosides also modulate acetylcholine release and the level of choline acetyl transferase (ChAT). Rb1 and Rg1 can modulate acetylcholine release and re-uptake determined with rat hippocampal slices [51] and the number of choline uptake sites determined by [³H] hemicholinium-3 binding experiments, especially in the hippocampus and to a lesser extent in cortex when it administered at least three days [52]. They also increased choline acetyltransferase levels in rodent brains which was determined by *in situ* hybridization in basal forebrain [53] as well as the level of acetylcholine in the brain [54], although other reports suggested Rg1 did not show any effects on ChAT activity [51]. Interestingly, Aβ(25-35)-induced suppression of the K^+-evoked [³H]-acetylcholine release from the rat hippocampal slices was effectively reversed by Rb1 but not by Rg1 in cholinergic synapse [55]. Taken together, these data suggest that Rb1 is the principal components regulating acetylcholine dynamics in brain.

Human clinical trials

In healthy volunteers, acute or chronic treatment of ginseng extracts produced both positive and negative results in cognitive functional tests (for a review, see [6,56]), preventing a generalized conclusion on the psychoactive properties of ginseng. Nevertheless, a few clinical trials have been conducted regarding the efficacy of ginseng or ginsenosides on AD. In 12 wk, open-label clinical trial, Heo et al. [57] treated AD patients with low or high concentration of Korean red ginseng extracts for 12 wk. The congnitive function of patients was assessed using the Alzheimer's Disease Assessment Scale, Korean version of the Mini-Mental Status Examination and Clinical Dementia Rating scale at the end of the 12 wk study period and high concentration of Korean red ginseng extracts treated group showed either a tendency or statistically significant improvement as compared with control group. The same group of researchers elaborated further with more patients and reported that 12 wk treatment of encapsulated *P. ginseng* powder (4.5 g/d) increased cognitive performance and the discontinuation of ginseng gradually decreased the congnitive performance back to control level [58]. Although the number of subjects is relatively small, the results suggest the potential of therapeutic significance of ginseng compounds in AD.

Currently available drugs and many of the experimental reagents against AD are generally symptomatic treatment and disease modifying medication is eagerly anticipated. In general, aggregation blockers and reagents effective for the Aβ dynamics in brain as well as drugs targeting Aβ production and clearance are expected to possess disease modifying potentials in some extents. Some of ginseng components are suitable for this criteria but the investigation in this field still in its infancy albeit numerous reports suggesting the beneficial effects on cognition and neuroprotection. In addition, some ginsenosides seemingly have multiple site of action, which make them ideal candidates for the next generation AD therapeutics. Future will tell, with unceasing efforts from existing researchers as well as new investigators in this field, whether the multi-faceted effects of ginsenosides on AD will be proven successful in the long run (Fig. 1).

PARKINSON'S DISEASE

Mainly due to the strong antioxidant effects and neuroprotective effects of ginseng and related compounds, many researchers investigated the effect of ginseng on neuroprotection in culture or animal models of PD. Some of the early studies using cultured neuronal cell lines such as PC12 suggested ginseng and ginsenosides provided anti-oxidant effects thereby protecting the cells from oxidant injury induced by dopamine [59], hydrogen peroxide [60] or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Treatment of dopamine in a concentration of 0.15 to 0.45 mM for 24 h induced apoptotic cell death of PC12 cells and the pretreatment of ginsenoside Rg1 protected apoptotic cell death. Ginsenoside Rg1 reduced the generation of dopamine-induced reactive oxygen species, iNOS induction and NO release, and the release of mitochondrial cytochrome *c* into the cytosol, and subsequently inhibited the activation of caspase-3 [59].

Some researchers also used primary dopaminergic cultures obtained from embryonic mouse mesencephalon and showed partial neuroprotective effects of ginsenoside Rg1 and Rb1 as evidenced by inhibition of decreased neurite length or number induced by a toxic metabolite of MPTP, 1-methyl-4-phenylpyridinium (MPP^+) treatment [61]. Somewhat bigger neuroprotective effects of ginsenoside Rg1 has also been demonstrated in reducing MPTP-induced substantia nigra neuronal loss in C57/BL6 mice, possibly via increased level of glutathione and superoxide dismutase activity [62]. Rg1 also inhibited MPTP-induced overload of iron and modulation of the expression of iron transporters such as divalent metal transporter and ferroportin1 in the substantia nigra [63]. The activity and level of iron transporters is regulated
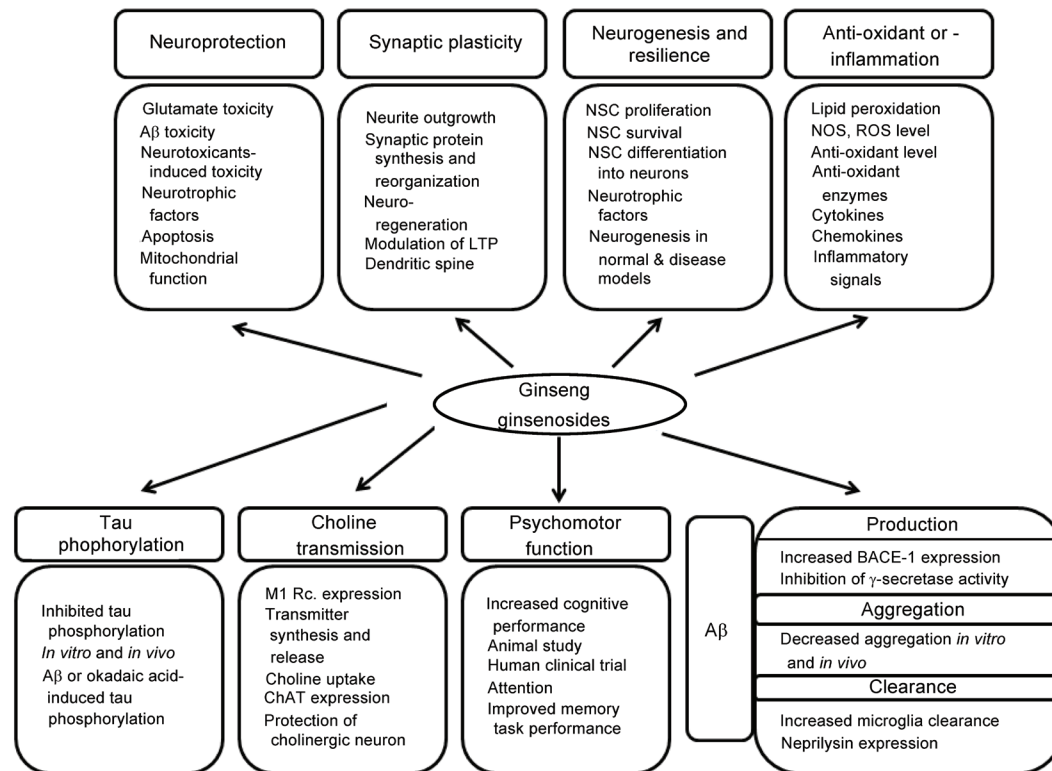
Fig. 1. Multiple therapeutic targets of ginseng and ginsenosides against Alzheimer's disease (AD). Only targets showing beneficial effects by either ginseng extracts, total saponins or individual ginsenoside have been shown in this figure. The multi-target action of ginseng against AD along with careful selection of ideal combination of active principles may provide disease modifying therapeutic agents with superior therapeutic profile and less adverse effects. LTP, long term potentiation; NSC, neural stem cell; NOS, nitric oxide synthase; ROS, reactive oxygen species; ChAT, choline acetyl transferase; BACE-1, β-site APP-cleaving enzyme 1.

by the IRE dependent transcriptional control as well as inhibition of iron regulator protein [64], which seems to be mediated by the regulation of ROS-NF-κB pathway [65]. Consistent with these results, it has been reported that panaxatriol saponins extracted from *P. notoginseng* induced thioredoxin-1 and protect PC12 cells or Kunming mice from MPP$^+$ or MPTP-induced toxicity, which was determined by MTT assay, LDH release and behavioral assays such as locomotor activity test and traction test [66,67]. Similar neuroprotective effects was also reported using rotenone model of neurotoxicity using primary dopaminergic neuron [68], which involves inhibition of mitochondrial apoptotic pathway, possibly via the modulation of glucocorticoid receptor and PI3K/Akt pathway. Involvement of Akt pathway in the modulation of neuronal survival by Rg1 against 6-hydroxydopamine (6-OHDA)-induced cell death was also reported in a study using MES23.5 cells [69]. Rg1 modulated 6-OHDA-induced loss of mitochondrial membrane potential and apoptotic protein expression in human neuroblastoma SK-N-SH cells via modulation of estrogen receptor as evidenced by increased estrogen responsive element

(ERE)-luciferase activity by Rg1 treatment in cells transfected with the ERE-luciferase reporter construct [70], suggesting the phytoestrogen-like effect of Rg1. Pharmacological study also suggested the involvement and possible crosstalk between ER and insulin-like growth factor receptor pathways in Rg1-mediated neuroprotection in 6-OHDA treated SK-N-SH cells [70]. Similar findings were confirmed *in vivo* using 6-OHDA lesion model by unilaterally injecting 6-OHDA into the medial forebrain bundle of ovariectomized Wistar rats [71].

In spite of seemingly strong evidence that ginsenoside Rg1 shows strong antioxidant effects in these PD models, a recent study suggested that individual ginsenosides such as Rb1, Rg1, and Re, have stimulus-dependent effects on the regulation of CD40 expression and virtually have no effects on NO production in N9 microglia, while *P. notoginseng* extracts showed strong inhibitory effects on CD40 expression, cytokine expression, NO production, and chemokine receptor expression regardless of the identity of immunological stimulus either by TRL ligands such as LPS and poly I:C, or by cytokine such as IFN-γ, suggesting it may be the combination of different

ginsenosides but not a single ginsenosides that provide strong anti-inflammatory effects against TRL ligand or cytokine stimulation of microglia [72]. In this study, it is also suggested that the anti-inflammatory effects of *P. notoginseng* extracts is not mediated by glucocorticoid receptor given that a pharmacological inhibitor of glucocorticoid receptor, RU-486, failed to reverse the anti-inflammatory effects of *P. notoginseng* extracts [72].

Animals received oral administration of *P. ginseng* extract G115 10 d prior to and/or following exposure (total 20 d) to the MPTP in mice, or MPP$^+$ in rats showed significantly fewer tyrosine hydroxylase (TH)-positive cell loss along with the reduction of apomorphine-induced contralateral rotations [73]. The lowest effective dose was 75 mg/kg/d and 200 or 500 mg/kg/d almost completely abolished the dopaminergic neural cell death in substantia nigra. Interestingly, the administration of G115 can be delayed until 2 d after MPP$^+$ administration, which still showed modest protective effects [73]. The delayed protection conferred by G115 is not likely due to blockade of neurotoxin uptake. Rather, the authors suggested the neurotrophic effects of ginseng such as the induction of NGF [53,74] may underlie the observed neuroprotective effects.

Although the majority of PD etiology is believed to be sporadic, genetic defects also contribute in the pathogenesis of PD and the animal models based on the genetic modulation of key genes involved in PD pathogenesis such as LRRK2 and α-synuclein found in autosomal-dominant PD as well as parkin, DJ-1, and PINK1 responsible for autosomal-recessive PD, provided insight into the molecular mechanisms of PD and new opportunities to design and develop new therapeutic agents for this devastating disease [75]. The investigation of the therapeutic effects and molecular and cellular mechanisms of ginseng on these animal models will provide further evidence of the efficacy of ginseng in PD.

OTHER NEURODEGENERATIVE DISORDERS

Huntington's disease
HD is an autosomal dominant, inherited disorder characterized by progressive neurodegeneration resulting in motor abnormalities, including chorea and psychiatric disturbance with gradual dementia. The characteristic pathological feature of HD is a polyglutamine expansion in huntingtin and the loss of medium spiny neurons in the striatum, although the exact mechanism of pathophysiology needs to be clarified. HD is an incurable disease, which needs the development of effective therapeutic

reagents. Using *in vitro* culture of medium spiny neuron of striatum obtained from the YAC128HD mouse model, Wu et al. [76] tested ginsenosides such as Rb1, Rc, Rd, Re, Rg3, Rg5, Rh1 as well as Re and Rd mixture, Rk1 and Rg5 mixture, and Rh4 and Rk3 mixture. The authors reported that nanomolar concentrations of ginsenoside Rb1 and Rc and micromolar concentration of Rg5 effectively protected YAC128 medium spiny neurons from glutamate-induced toxicity, which was mediated by regulation of intracellular calcium concentration. Other ginsenosides were without effects. Unfortunately, follow up studies examining the effects of those ginsenosides on other models of HD as well as the effects in animal models are not available yet, which will substantiate the efforts to develop HD medication based on ginseng and related products.

Amyotrophic lateral sclerosis
ALS is a degenerating motor neuron disease characterized by muscle weakness and paralysis in affected individuals. The correct pathophysiology is currently unknown with which most of the cases are sporadic with a few identified genetic risk factors. Albeit these lack of pathophiological information of the disease, it has been reported that mutations in the gene that produces the Cu/Zn superoxide dismutase (SOD1) enzyme were highly associated with familial cases of ALS and experimental animals with SOD1 mutation showed ALS-like phenotypes. Using B6SJL-TgN(SOD1-G93A)1Gur transgenic mice, the efficacy of ginseng extracts, which was given in drinking water, was tested on onset of motor symptoms as well as survival rates of the mice [77]. Although there was no dose-response relationship (40 and 80 mg/kg), ginseng extracts provided weak but significant delay in the onset of ALS symptoms when it administered from age 30 d and onwards [77]. Whether the protective effects are related to the anti-oxidant effects (and thereby neuroprotection) or neurotrophic effects of ginseng remains to be determined.

CEREBRAL ISCHEMIA

Protective effects of ginseng and ginsenosides
There are dozens of studies indicating ginseng extracts or ginsenosides obtained from various ginseng species provide functional as well as neuroanatomical protection from ischemic stroke (Table 1). Various experimental models has been used including middle cerebral artery occlusion (focal transient ischemia), four-vessel or bilateral common carotid artery occlusion (global ischemia)

Table 1. Effects of ginseng or ginsenosides on experimental ischemic stroke

Experimental scheme	Species	Treatment protocol	End point	Reference
Focal ischemia				
MCAO (30 min)	Rat (Swiss albino adult male, 200-250 g)	Pre-treated with Korean ginseng tea (350 mg/kg given orally for 10 d)	Histopathology Brain weight and water contents Oxidative stress	[78]
MCAO MCAO MCAO (60 min)	SD (270-320 g) C57BL/6 (16-18 mo)	Rd (50 mg/kg), i.p. 30 min pretreatment Rd (10-50 mg/kg), same as above Rd (10-50 mg/kg), same as above	Infarct volume, mitochondrial function, apoptosis Inflammatory responses, oxidative stress Oxidative stress	[89] [90] [85]
MCAO (2 h)	SD (250-300 g)	Rd (10 mg/kg) i.p. injected 15 min before MCAO	Expression of cation channels TRPM7 and ASIC1a	[91]
MCAO (2 h)	Rat	PNS (50 mg/kg), i.p. 2 h after reperfusion	Expression of intercellular adhesion molecule-1 Brain neutrophil infiltration Brain edema, neurological score, infarct size	[31] [92]
MCAO (2 h)	SD (300 g)	KRG (100 mg/kg/d) after reperfusion. Once daily for 1 wk. Oral treatment	Infarct volume, neurological score, serum cytokine level	[93]
MCAO (2 h)	SD (270-320 g)	PNS (25 mg/kg), i.p. 5 min before and 12 h, 24 h and 36 h after MCAO	Apoptosis (TUNEL staining, caspase 1, 3 expresion)	[94]
MCAO (2 h)	SD (250 g)	Intranasal Rb1 (1.25 mg/kg or 12.5 mg/kg)	Infarct volume, neuronal density Autophagic marker protein level (LC3, Beclin 1) after 24 h reperfusion	[95]
MCAO (2 h)	SD (220–250 g)	Rb1 (12.5 mg/kg/d) intranasal once daily, 7 d before MCAO	Neuroinflammation (microglial activity, increased production of TNF-α, IL-6, and activation of NF-κB)	[96]
MCAO (2 h)	SD (270-280 g)	Rh2, 100 mg/kg, oral treatment immediately prior to reperfusion	Infarct volume, neurological score after 22 h reperfusion	[88]
MCAO (2 h)	SD (250-280 g)	Black ginseng extracts (100 or 400 mg/kg), oral (daily for 2 wk) after ischemia	Neuronal density Learning and memory (Morris water maze) Cholinergic system (ChAT), nNOS expression in hippocampus	[97]
MCAO (30 min)	C57BL/6 mice (10-11 weeks old)	Compound K (30 mg/kg i.p.) 4 d before ischemia	Infarct volume, microglial activation	[30]
MCAO	SD (270-305 g)	PGE (200 mg/kg), oral treatment for 1 wk after ischemia	Infarct volume, behaviors after 15 d (rota-rod and adhesive removal test), activating astrocyte, neuronal death, and apoptotic cell death	[98]
MCAO (permanent)	SHR-SP (250-300 g)	Dihydroginsenoside Rb1 (dgRb1) i.v. after ischemia and then infused using osmotic pump (0.6 or 6 g/d)	Infarct volume (24 h and 4 wk) Learning and memory (Morris water maze)	[99] [87]
		Rb1, i.v. immediately or 2 h after ischemia, then chronic infusion. as above (6, 60, 3000 or 12,000 g/d)	Infarct volume, learning and memory (Morris water maze) and neuronal staining	[100]
MCAO (90 min)	SD (280-320 g)	Rb1, i.v. 2 h before or immediately after MCAO and then chronic infusion as above PNE (50 mg/kg) i.p. 2 h after the onset of MCAO	Infarct volume and microglial activation 24 h after reperfusion	[101]
MCAO (1 h)	SD (250-300 g)	Rg2 (2.5, 5 and 10 mg/kg), 15 min or 24 h after ischemia, i.v. into tail vein	Neuronal density, infarct volume, Neurological score, Y-maze test, Expression of apoptosis-related proteins	[102]
MCAO (2 h)	Rat	Rb1 (10-40 mg/kg), i.v. 30 min before or immediately after MCAO	infarct size, neurologic deficit, contents of calcium and potassium in the infarct	[103]
MCAO (permanent)	Rat	Rb1 (40 mg/kg), i.v.	infarct size, neurologic deficit, contents of calcium and potassium in the infarct	[103]
MCAO (permanent)	Wistar	PGS (25mg/kg/d), i.p. 3 day before ischemia until 1-14 d	Neurological score Neurogenesis (BrdU and NeuN staining)	[104]
Global ischemia				
4-VO (10 min)	Wistar, male, 160-180 g	PGE (Ethanolic, 200 mg/kg), i.p. 0 and 10 min after ischemia	Hippocampal neuronal protection (Nissl staining, lipid peroxidation)	[79]
BCCaO (30 min)	Rat (Swiss albino adult male, 350 g)	pre-treated with Korean ginseng tea (350 mg/kg given orally for 10 d)	Histopathology, Brain weight and water contents Oxidative stress	[78]
BCCaO (5 min)	Gerbil (male, 70-80 g)	Pretreatment (7 d) red ginseng powder (oral, 1.5g/kg), total saponin (i.p. 100 mg/kg), Rb1 (i.p. 20 mg/kg). Rg1 and Ro were ineffective	Hippocampal CA1 protection. Electron microscopy Memory improvement (passive avoidance)	[81]
BCCaO (3- 3.5 min)	Gerbil (male, 70-80 g)	Rb1 (2.5 or 25 ng), i.c.v. injection immediately after ischemia	Neurological deficit (passive avoidance test) Neuronal density in hippocampal CA1 field	[105]

Table 1. (Continued)

Experimental scheme	Species	Treatment protocol	End point	Reference
BCCaO (3 min)	Gerbil (male, 70-80 g)	Rb1 (2.5 or 25 ng), i.c.v. injection into the left lateral ventricle and then Rb1 (60 or 600 ng/day) was continuously infused for 7 days into ventricles	TUNEL staining Bcl-xL expression	[87]
4-VO (40 min)	Rat	Ginsenosides Rb + R0 100 mg/kg i.v. 30 min before ischemia	prostacyclin synthesis, thromboxane A_2 formation and lipid peroxidation, creatine phosphokinase, brain edema (1 h reperfusion)	[80]
4-VO	Rat	Ginseng (200 mg/kg/d) 1 wk before the occlusion	Recovery of local cerebral glucose utilization	[106]
BCCaO + right MCAO (90 min)	SD	PNE (water), oral, 0.5 g/kg/d, 3 d a week for 4 wk after the operation	Neurological score, learning and memory (eight-arm radial maze), BDNF, β-secretase and immunological markers	[107]
In vitro				
OGD (2 h)	Hippocampal neuron (E18, SD)	Rd (0.1-10 μM) during and after OGD	Cell death, oxidative stress, mitochondrial function	[84]
OGD (10 min)	Acute hippocampal slice (adult Kunming mice)	Rb3 (10-50 μM) 20 min prior to and during OGD	The recovery of the amplitude of population spike (PS) in the stratum pyramidale	[108]
Hypoxia (0.1% O_2)	Human neuroblastoma cells SK-N-MC	PGE, 100 mg/mL, 6 h	Hypoxia-induced cell death Gene expression profile (human 8K microarray)	[109]
OGD (6 h)	Primary hippocampal neural stem cell (SD, 1 day old)	PNS (4.4 μg/mL-2.2 mg/mL)	Proliferation (BrdU) Differentiation into neuron and glia	[110]
OGD (4 h)	PC12	Rb3 (0.1-10 M)	Cell death, apoptosis, calcium elevation, caspases and apoptosis related protein expression	[111]

The effects of *Panax ginseng* or *P. notoginseng* either in extracts or total saponin forms as well as ginsenosides obtained from them on animal or culture model of ischemia were summarized. Experimental scheme was categorized as focal and global ischemia as well as *in vitro* culture model. The treatment protocols of ginseng and experimental end points in each experiment were also summarized with relevant references. MCAO, middle cerebral artery occlusion; SD, Sprague-Dawley rats; PNS, *P. notoginseng* saponins; KRG, Korean red ginseng; TNF, tumor necrosis factor; IL, interleukin; ChAT, choline acetyl transferase; nNOS; neuronal nitric oxide synthase; PGE, *P. ginseng* extracts; SHR-SP, spontaneously hypertensive rats-stroke prone; PNE, *P. notoginseng* extracts; PGS, *P. ginseng* saponins; 4-VO, four-vessel occlusion; BCCaO, bilateral (common) carotid artery occlusion; OGD, oxygen glucose deprivation.

in rats and mice [78-80], transient forebrain ischemia by short-term transient bilateral common carotid artery ligation in gerbil [81], and hypoxic-ischemic brain injury model in neonatal rats [82], in addition to the *in vitro* oxygen glucose deprivation or glutamate-induced toxicity model [83,84]. For example, ginsenosides Rd [85], Rg3 [86], Rb and Ro [80,87] as well as ginsenoside Rh2 reduced ischemic brain injury in rats or mice [88]. In 5-min transient forebrain ischemia model of gerbil, ginsenoside Rb1 significantly prolonged the response latency of ischemic gerbils in passive avoidance test and rescued a significant number of ischemic CA1 pyramidal neurons, whereas ginisenosides Rg1 and Ro were ineffective.

Anti-ischemic mechanism of ginseng and ginsenosides

Although part of the reason that much of the pharmacological intervention study against neurological diseases using ginseng and/or ginsenosides are focused on cerebral ischemia are related to the ginseng's potent anti-inflammatory and anti-oxidative activity in microglia and astrocytes as well as in insulted brain [30,80,101,112],

many other studies suggest that other mechanisms are also involved in the potent neuroprotective or neuro-restorative actions such as regulation of channel proteins including TRM, ASIC and NMDA receptors [91], Potassium channel [113], Na channel [114], inhibition of mitochondrial permeability transition pores [86], regulation of anti-apoptotic proteins [87], changes in receptor binding activity including NMDA and GABA receptors [115], defense against excessive endoplasmic reticulum stress [116], regulation of angiogenesis and the expression of vascular endothelial growth factor [99,117,118], cerebral vasorelaxation possibly via NO pathway [119], and induction of hypoxia inducible factor-1α [120], which may affects cell survival, angiogenesis, and neurogenesis after ischemic injury.

In one study, rats were subjected to 45 min of myocardial ischemia followed by 120 min of reperfusion and 10 min preconditioning with ginsenoside Rb1 right before the induction of ischemia increased Akt phosphorylation, probably through the activation of the PI3K pathway [121]. PI3K/Akt pathway has been shown to be essential in the regulation of cell survival as well as infarct size

reduction, which seems to be plausible molecular switch mediating the effects of ginseng in ischemic stroke in brain as well.

Excessive sodium influx is one of the factors involved in neuronal damage in ischemic conditions. In tsA201 cells transfected with cDNA expressing α subunits of the Brain$_{2a}$ Na$^+$ channel, the whole-cell patch clamp experiments revealed that American ginseng (*P. quinquefolius*) extract or ginsenoside Rb1, tonically and reversibly blocked the channel in a concentration- and voltage-dependent manner [114]. Ginsenoside Rb1 stimulated the expression of the mitochondrion-associated antiapoptotic factor Bcl-x(L) *in vitro* as well as in stroke prone spontaneously hypertensive rats (SP-SHR) subjected to permanent focal cerebral ischemia [87]. Interestingly, Stat5 responsive element in the bcl-x promoter became active in response to Rb1 treatment suggesting the possible role of Rb1 in the regulation of cell death pathway thereby providing neuroprotection in ischemic condition [87].

Ginsenosides can regulate the expression of factors important in the pathogenesis and prognosis of ischemia such as HIF-1α. The induction of HIF-1α by ginsenosides is independent of hypoxia, for example, ginsenoside Rg1 regulated the induction of HIF-1α even in normoxic condition [120]. Interestingly, the induction is not regulated by transcriptional regulation evidenced by no changes in the level of HIF-1α mRNA. Rather, the induction is governed by translational up-regulation of HIF-1α in a mechanism dependent on the activation of PI3K and S6K pathway. LY294002 or rapamycin, inhibitors of PI3K and S6K pathway, respectively, attenuated Rg1-mediated induction of HIF-1α, suggesting the essential role of these pathways in the ginsenoside-mediated regulation of HIF-1α. Considering the importance of mTOR pathway in several psychiatric disorders, this data is potentially interesting to investigate whether regulation of mTOR is involved in the regulation of psychiatric disorders by ginseng.

Ginseng and ginsenosides may affect neurogenesis in the ischemic brain. It has been suggested that ginsenoside Rg1 and Rb1 increase proliferation and differentiation of neural progenitor cells in dentate gyrus of hippocampus of normal adult mice and gerbils subjected to global ischemia suggesting the usefulness of the ginsenosides in neurodegenerative diseases such as AD as well as neurological insults condition such as cerebral ischemia (for a review, see [16]). *P. notoginseng* extracts increased neural stem cell (NSC) proliferation and the expression of nestin/BrdU, and also enhanced Tuj-1, vimentin, and nestin mRNA expressions in hippocampal NSCs isolated from newborn rat hippocampus with similar effects in oxygen glucose deprived NSCs, suggesting possible neuroprotective role of ginseng by providing increased neurogenesis in ischemic or neurodegenerative conditions [110]. Similarly, when total ginseng total saponin (GTS) was intraperitoneally administered from 3 d before ischemia until 14 d after it, the number of BrdU$^+$ cells and BrdU$^+$/NeuN$^+$ cells in GTS group were significantly higher than those in saline-treated group in the ipsilateral subventricular zone and in the ipsilateral infarct area after MCAO [104]. Importantly, the increase of the number of BrdU$^+$/NeuN$^+$ cells highly correlated with the decrease of neurological scores, suggesting the therapeutic role of the increased neurogenesis by GTS in ischemic stroke.

More recently, it has been suggested that the neuroprotective effects of Rb3 in oxygen-glucose deprived neuron might be related to their effects on GABA$_A$ receptor [108]. It remains to be determined whether the GABAergic effects of Rb3 are dependent on the modulation of steroid binding sites on GABA$_A$ receptor.

Unfortunately, most of the studies in this field are explanatory on the therapeutic potential of ginseng compounds with little explanation of mechanism of action, especially, the causal relationship of the molecular or biological changes induced by ginseng on therapeutic action.

Recently, Yue et al. [122] reported that eighteen proteins involved in pathways including energy metabolism, lipid metabolism, muscle contraction, heat shock stress, and cell survival and proliferation has been changed in ischemia-reperfusion induced injury model of rat treated with notoginsengnosides with or without salvianolic acids suggesting these proteins might be the possible protein targets in their cardioprotective effects. Some of these proteins are also implicated in neuroprotection as well as ischemia-induced neuronal cell death pathway, which may prompts further study using cerebral ischemia model.

Although it has been reported that ginseng regulates a set of gene which is involved in cellular physiologic response related genes such as MPHOSPH10, IMP-3 and SDCBP, in hypoxic human neuroblastoma cells SK-N-MC in an experiment using 8K human cDNA microarray analysis [109], systemic investigation trying to find out cellular responses affected by ginseng using metabolomics, proteomics, and genomics approach in ischemic condition is scarce. In this sense, it is noteworthy that two studies investigated the effects of ginseng in gene expression profile after immobilization stress (Gene Expression Omnibus [GEO] accession number GSE12656) and the

role of micro RNA in ginsenoside-Rg1-induced Angio-genesis (GSE17541) [117,118], with their data submitted in GEO.

Clinical trials and human study

There's not much carefully designed, controlled clinical trials using ginseng on the possible effects on ischemic stroke. Sanchi, the dried root of *P. notoginseng*, is one of the most widely used herbal medicines for ischemic stroke in China and Chen et al. [123] examined available clinical reports about the effectiveness and safety of Sanchi and concluded that Sanchi appears to be beneficial and safe for acute ischemic stroke. However, as the authors stated in their review, the small sample size and inferior quality of study design and performance in some of those studies, prevented a definite conclusion, which dictates more well-designed randomized controlled trials. Recently, one clinical trial has suggested that co-treatment of Sanchi capsule with low concentration of aspirine significantly ameliorated neurological deficit and impairments in activities of daily living in a study conducted with 140 human patients hospitalized in four hospitals in China over the year 2004 to 2006 [124].

Kinetics and related issues

In most of the studies, ginseng extracts or ginsenosides were treated at least 30 min before the induction of ischemia [80,81,96,106]. In many cases, post ischemic treatment of ginseng or ginsenoside was not effective to rescue the ischemic brain [81], which limits the therapeutic applicability of the ginseng and related products. However, the post-ischemic infusion of ginsenoside Rg1 provided neuroprotection as well as functional recovery determined by Morris water maze after permanent middle cerebral artery occlusion in SP-SHR [87]. In some cases, ginseng containing prescription such as Sheng-mai San also effectively suppressed the oxidative stress determined by TBARS formation even when it was administered after 45 min reperfusion following ischemia, although individual components of the prescription did not provided a protective effects [125]. Recently, it was also reported that treatment of Korean red ginseng (KRG) after ischemic injury protected brain from neurological deficits [93]. In this case, the authors used adult male Sprague-Dawley rats to induce transient middle cerebral artery occlusion for two hours and then the rats were fed KRG extract (100 mg/kg/d per orally) or saline after reperfusion. After seven day treatment of KRG extracts, both brain infarct volume as well as neurological score was improved by KRG treatment and the elevated se-

rum levels of TNF-α, IL-1β, and IL-6 were attenuated by KRG with concomitant increase in serum level of IL-10 [93], which has been argued to be responsible for the improved ischemic outcome with oral-treatment of KRG extract. In one study using transient focal cerebral ischemia (MCAO) model in rats, *P. notoginseng* saponin (PNS) was administered at different time points after MCAO and the authors argued that the administration of PNS at 3 to 4 h after onset of ischemia significantly reduced neurological deficit score, infarct size and brain edema with decreasing effects at 5 h after the onset of ischemia and no effects at 6 h suggesting the therapeutic window until 5 h in rat model [92].

Intravenous injection of Rb1 before or with MCAO at dose range of 10 to 40 mg/kg in rat reduced infarct size and neurological deficit score [103] but not with 40 mg/kg PNS [126], suggesting the use of correct combination or active principle of ginsenosides might provide lower therapeutic dose for the treatment of ischemia.

Another point of concern in the comparison of different reports regarding the effectiveness of ginseng is the route of administration. Many of studies used IV injection of ginsenosides for the study of short term effects of ginsenosides [80], while others used oral administration route to study the long term effects or the restorative potential of ginseng. Even in some cases, ginsenoside was administered by intracerebroventricular infusion [105]. Intranasal delivery of ginsenoside Rb1 targets the brain and ameliorates cerebral ischemia/reperfusion injury in rats [95], which might be a good route of administration to overcome the blocking effects of blood brain barrier against ginsenoside. In this study, it was argued that a local bioavailability of 10.28% to 32.48% and drug targeting index (which means the availability of Rb1 in brain compared with IV injection) of 7.35 to 23.22 in different brain regions. Intranasal Rb1 was determined to be brain-targeting and might be an efficient way to deliver ginsenosides in cerebral ischemia.

DEPRESSION

Several reports suggested that traditional medicinal formulation containing ginseng may be effective in ameliorating the symptoms of depression in humans and animal models [127-129]. In addition, total ginseng extracts or total saponin preparation has been reported to be effective in combating depression-like behaviors evaluated using animal models such as tail suspension test, forced swimming test, injection of corticosterone, chronic unpredictable mild stress, and menopausal depressive-

like state in female mice induced by ovariectomy or morphine withdrawal-induced depression behavior [130-136]. Similar anti-depressive effects of chronic oral KRG extracts administration on human postmenopausal patients with climacteric syndrome have also been reported [137].

Based on the anti-depressant effects of orally administered ginseng, Xu et al. [138] examined the effects of intestinal metabolite of ginseng, 20(S)-protopanaxadiol (code name S111) on depressive behavior in experimental animals, which was tested in tail suspension test and forced swimming test as well as olfactory bulbectomy depression model in rats. Interestingly, the antidepressant-like activity was comparable to that of fluoxetine and S111 increased monoamine neurotransmitters in the brain and showed modest inhibitory effects against neurotransmitter reuptake *in vitro*. In contrast to fluoxetine, S111 inhibited oxidative stress and reduced serum corticosterone level in olfactory bulbectomized animals suggesting S111 modulates depression-like behavior by regulating multiple targets including both central and peripheral inflammation, regulation of hypothalamic corticotrophin-releasing factor (CRF) and Neuropeptide Y (NPY) expression and regulation of glucocorticoid receptor and BDNF expression as well as neurofilament-L in hippocampus [133-135,139]. Many of these results suggest that ginseng and ginsenosides regulate brain neurotransmitter turnover and hypothalamic- pituitary-adrenal axis.

Ginsenosides may affect adult neurogenesis which is reminiscent of the effects of fluoxetine on hippocampal neurogenesis implicating a possible link of the ginseng and related compounds on anti-depressant action. Actually, in a recent experiment using chronic mild stress model of depression in mice, it has been reported that Rg1 up-regulated the BDNF signaling pathway in the hippocampus and reversed the decrease in dendritic spine density and hippocampal neurogenesis caused by chronic mild stress without affecting the monoaminergic system [15]. Recently, Yamada et al. [136] reported that Rg3 and compound K provided strong anti-depressant effects in ovariectomized animals which are blocked by 5-HT$_{2A}$ antagonist ritanserine suggesting additional molecular target in the treatment of depression by ginseng.

ANXIETY

In several different experimental paradigms to detect anxiety like behaviors such as open-field, elevated plus-maze tests, conflict behavior in thirsty rats and footshock-induced fighting in paired mice, chronic oral administration of ginseng extracts but not single acute administration of ginseng produced comparable anxiolytic activity as acute diazepam [140], which is suggested to be related with the modulation of monoamine oxidase activity. Using five day-old male chick, the effects of ginsenoside Rb1 on separation distress was evaluated, which provided robust effects of ginseng on anxiety level [141]. These results led the authors to draw the conclusion that nootropic hence the memory enhancing effects of ginseng is strongly associated with the anxiolytic effects. Among several different ginsenosides tested including Rb1, Rg1, Rg3-R, and Rg3-S, and the Rg5 and Rk, ginsenosides Rb1, Rg1, and the Rg5 and Rk mixture showed anxiolytic-like effects in elevated plus maze test [142]. Similar anxiolytic effects of Rb1 [143] or Rg3 and Rh2 was observed in separate sets of experiments [144]. Although the anxiolytic activity of ginsenosides may involve the action on GABA/Benzodiazepine receptors [144], ginsenosides inhibited locomotor activity to a lesser extent than diazepam, which may implicate the better side/adverse effect profile of ginsenosides as anxiolytic agents [142,145].

However, negative results are also available that did not observe any effects on anxiety or depression behavior even after 3 wk chronic treatment of several ginsenosides [146], which suggests that careful interpretation and more studies might be needed using multiple animal models and test paradigms including light/dark test, holeboard test, and isolation-induced aggressive test [145], which is reviewed in a recent article [147].

ADDICTION

Ginseng has been believed to reduce the behavioral and physiological responses against psychostimulants and other drug of abuse such as opioids and to ameliorate the withdrawal symptoms. Pseudoginsenoside-F(11), a saponin contained in American ginseng, effectively attenuated methamphetamine-induced behavioral and neurochemical toxicities such as anxiety, depression, and memory deficits and alterations of monoamine contents in mice brain [148].

When the effects of total ginseng saponins were examined on presynaptic nicotine-induced dopamine (DA) release in the striatum of freely moving rats using *in vivo* microdialysis technique and on the *in vitro* and *in vivo* binding of [^{3}H]raclopride to DA D$_2$ receptors, inhibition of nicotine-induced DA release and D$_2$ receptor binding was observed along with behavioral inhibition of

nicotine-induced sensitization [149]. Similar results were observed with repeated cocaine administration. Pretreatment with GTS before the daily intraperitoneal injections of cocaine (15 mg/kg,) significantly inhibited the repeated cocaine-induced behavioral sensitization as well as the c-Fos expression in the core and shell of nucleus accumbens. In addition, pretreatment with GTS significantly decreased the repeated cocaine-induced increase in DA release in the nucleus accumbens as determined by *in vivo* microdialysis [150]. Similarly, Using real-time measurements of the extracellular DA concentrations by real-time fast-scan cyclic voltammetry in slices of rat brain nucleus accumbens, it has been demonstrated that co-treatment of GTS inhibited the release enhancement of DA and subsequently prevented the rebound increase during acute withdrawal of cocaine without affecting the cocaine-mediated DA uptake [151].

In addition, morphine withdrawal-induced anxiety and depression-like behavior were effectively inhibited by wild ginseng extracts by modulating hypothalamic expression of CRF and NPY [133]. Moreover, the same group of researchers have reported that wild ginseng extracts effectively attenuated morphine withdrawal-induced behavioral sensitization along with modulation of c-Fos expression in nucleus accumbens and TH expression in ventral tegmental area suggesting the possible involvement of ginseng in the modulation of dopaminergic nervous system activity during morphine withdrawal [152].

The signaling pathway leading to the decreased DA release and the neurobiological targets of ginseng mediating the up/down-regulation of proteins involved in the addiction subsequent to the withdrawal of drug of abuse remains to be determined, although regulation of intracellular ion influx including calcium seems to be one of the plausible targets.

OTHER PSYCHIATRIC DISORDERS

In a rat model of epileptic seizure, pentylenetetrazole was injected intraperitoneally at the dose of 30 mg/kg, on alternate days to obtain generalized tonic-clonic convulsions in rats and pretreatment of *P. ginseng* protected the rats from epileptic seizure [153]. Based on the fast inhibition of ginseng total saponins and ginsenoside Rg3 on NMDA receptor-mediated $[Ca^{2+}]_i$ in cultured hippocampal neurons, Kim and Rhim [154] determined that ginseng total saponins and ginsenoside Rg3 inhibited Mg^{2+} free-induced increase of $[Ca^{2+}]_i$ and spontaneous $[Ca^{2+}]_i$ oscillations in cultured rat hippocampal neurons suggesting ginseng may be effective in correcting the

epileptiform discharge induced by excitatory/inhibitory imbalance. In an experiments using three different chemical seizure inducing agents, i.e., pentylenetetrazole, kainic acid, and pilocarpine, American ginseng provided protective effects against seizure [155]. Albeit the root preparation or leaves/stem preparation provided a marginal range of protection, the partially purified extracts that concentrate Rb ginsenosides (Rb extract) had a dose-dependent anticonvulsant effect in all three models of chemically induced seizures. Rb extracts also reduced neuronal stress induced by kainic acid as evidenced by the reduced immunohistochemical signal against heat shock protein 72 [155]. The same group of researchers expanded their efforts to identify active components in ginseng extracts and concluded that the mixtures of purified Rb1 and Rb3 provided most robust anti-epileptic activity [156]. Interestingly, no single ginsenoside provided enough anti-epileptic and neuroprotective effects, which suggest that the combination of different ginsenosides is needed for optimal results [156].

Ginseng has been suggested to be effective in schizopherinic patients. In a 4 wk double-blind, placebo-controlled study using HT1001, a proprietary North American ginseng extract, improved working memory in schizophrenic patients [157]. In addition to the verbal and visual working memory improvement, HT101 reduced extrapyramidal symptoms after 4 wk treatment suggesting HT1001 might be effective in treating schizophrenia as well as to reduce the side effects of currently available medications [157]. Similarly, *P. quinquefolius* showed various range of neurological effects in ketamine-induced experimental psychosis model in mice without severe extra-pyramidal side effects and catalepsy [158]. Increased glutamate contents and decreased DA and 5-HT contents are evident along with increased acetylcholine esterase and nitrate level, which may impose the need for further study.

NEURODEVELOPMENTAL DISORDERS

A recent drastic increase in prevalence of several neurodevelopmental diseases including ADHD and autism spectrum disorder (ASD) along with the relative lack of safe and efficient therapeutic agents in this field albeit the wide spread use of stimulant medication in the case of ADHD, necessitates the investigation whether ginseng has therapeutic potential in this group of diseases. Surprisingly, only a small number of investigations have been reported so far, mostly focused on ADHD. Using a combinatorial herbal medicine consists of American gin-

seng and *Ginko biloba*, 36 children ranging in age from 3 to 17 yr with ADHD was enrolled in open-label clinical study [159]. After 4 wk treatment of the herbal mixture, parents completed revised version of Conners' Parent Rating Scale and the authors reported that 44% to 74% of patients showed some kind of improvement either in social problem attributes or DSM-IV hyperactive-impulsive attribute [159]. The study hampers with the small number of subjects, and even with the initially promising results, no follow up study has been reported so far. Up to now, contradictory results have been reported about the possible effects of ginseng on hyperactive phenotype in experimental animals. Chronic oral administration of ginseng slightly decreased the activity in open field test while it did not produce any significant difference against hyperactivity induced by amphetamine [136], while others reported the attenuation of behavioral sensitization induced by chemical stimulants [138,139,142]. More recently, it has been also suggested that three ADHD inattentive type patients showed improvements in their hyperactivity and inattention symptoms after taking *P. ginseng* as judged by Conners' parent ratings [160]. Obviously, clinical studies with more number of patients as well as animal studies using relevant models and behavioral paradigms might be needed in this field [161].

ASD is a neurodevelopmental disorder characterized by the impairment in communication, social interaction, and repetitive behavior. Although it has been suggested that *P. ginseng* may have beneficial effects in the treatment of ASD patients in a preliminary study with human patients [162], no definite and elaborate study has been conducted in either animal and human studies. Interestingly, one recent article suggested that the active acidic polysaccharide portion of *P. ginseng* increased social engagement both in time and frequency in normal mice. The reason for increased engagement was majorly attributed to the increased non-aggressive engagement in mice which is interpreted being related to the anti-depressant effects of ginseng [163]. Combined with the fact that ginseng may have efficacy in seizure, anxiety and schizophrenia, investigating whether ginseng might have therapeutic effects in this devastating disorder would be helpful to devise tools for intervention against the otherwise non-curable disorder.

CONCLUSION

Ginseng and ginsenosides affect various aspects of neurodevelopmental disorder including AD and PD as well as neuropsychiatric disorders and even neuro-

developmental disorder. Even with the vast array of researches conducted during last two decades, it still needs elaboration on the molecular and cellular mechanism of action. Even in studies showing the effects on therapeutic targets, the causal relationship of the target modulation is not clear. Obviously, investigations using more pharmacological model systems as well as genetic model systems would be essential to unravel the therapeutic efficacy as well as molecular mechanisms. Recent progress in high-throughput measures to study biological processes such as omics technology would be beneficial in the field of ginseng research as well. Unresolved questions such as the obvious therapeutic efficacy even with the poor kinetic profiles of some ginsenosides after oral administration, are being approached in several ways, for example, demonstrating the therapeutic efficacy of ginsenoside metabolites such as compound K and devising new way of administration including intranasal administration. It is increasingly evident that not a single molecular target can explain all the pathophyiological features of a given neurological diseases. In many cases such as AD and ischemia, hope to develop a therapeutic agent based on a single molecular targets is almost coming to an end unless the ultimate new target is developed and available for those invincible disease. In this regard, the fact that ginseng affects seemingly a multiple number of targets regulating synaptic plasticity, neurogenesis, neuroprotection, neural transmission, and much more, is worthy of special attention. Finally, the comparison of pharmacological and therapeutic effects of different ginseng preparation needs standardization of preparation otherwise there's no way to improve our understanding of the differential effects of specific ginseng preparation on particular neurological disorders. With the unceasing efforts of the existing and forthcoming investigators in this field, future will tell us whether ginseng will provide effective tools to combat with AD, PD, ischemia and other neurological condition or disorders.

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