Ginsenosides and Their CNS Targets

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SUMMARY

Ginsenosides are a special group of triterpenoid saponins attributed to medical effects of ginseng. Therefore, they have been research targets over the last three decades to explain ginseng actions and a wealth of literature has been presented reporting on ginsenosides' effects on the human body. Recently, there is increasing evidence on beneficial effects of ginsenosides to the central nervous system (CNS). Using a wide range of *in vitro* and *in vivo* models, researchers have attributed these effects to specific pharmacological actions of ginsenosides on cerebral metabolism, oxidative stress and radical formation, neurotransmitter imbalance and membrane stabilizing effects, and even antiapoptotic effects. Modulating these particular mechanisms by ginsenosides has thus been reported to exert either general stimulatory effects on the brain functions or protecting the CNS against various disease conditions. In this review, we try to address the recently reported ginsenosides' actions on different CNS targets particularly those supporting possible therapeutic efficacies in CNS disorders and neurodegenerative diseases.

Introduction

Ginseng as a name refers to a group of slowly growing plants with fleshy roots belonging to the genus *Panax* in the family Araliaceae. Among them, *Panax ginseng* is the most famous and precious herbal medicine consumed worldwide [1]. Ginsenosides are unique triterpenoid saponins found exclusively in *Panax* species and up to now more than 150 naturally occurring ginsenosides have been isolated from roots, leaves, stems, fruits, and/or flower heads of ginseng [2–4]. All ginsenosides have a common four-ring hydrophobic steroid-like structure but with a different number of sugar moieties [5]. According to the number and position of these sugar moieties, ginsenosides are classified into two major groups: 20(*S*)-protopanaxadiol (PD) and 20(*S*)-protopanaxatriol (PT) saponins. The diversity of the sugar components between ginsenosides might be responsible for the specific action of each ginsenoside [6,7].

After discovering ginseng as a medical plant in Manchuria (China) over 5000 years ago, its whole roots were first taken as a food and 2000 years later, early Chinese used ginseng as a general tonic and adaptogen helping the body to resist the adverse influence of a wide range of physical, chemical, and biological factors and to restore homeostasis [8,9]. Since the middle of the last century, scientists in Asian and Western countries have paid great attention to ginseng research, which led to isolation and identification of ginsenosides which have been found to produce a wide

range of actions on different body systems. Recently, ginsenosides have been shown to produce a number of beneficial effects in the CNS [10]. These actions of ginsenosides are attributed to specific pharmacological effects on particular CNS targets. Modulation of these targets by ginsenosides found to stimulate the brain functions and induced protection against various disease conditions. This review was designed to address and discuss the recent reports dealt with effects of ginsenosides on different CNS targets particularly those that are associated with therapeutic efficacies in CNS disorders and neurodegenerative diseases.

Ginsenosides-Modulated CNS Targets Associated With Potentiating of Brain Functions

Ginsenosides Promote Neurogenesis

The dogma that mammalian CNS is an organ unable to regenerate has been challenged about 20 years ago when Reynolds and Weiss [11] published their pioneering work in *Science* about proliferation and differentiation of cells isolated from the striatum of adult mouse into neurons and astrocytes *in vitro*. Nowadays, it is fully accepted that adult neurogenesis occurs in the subgranular zone (SGZ) in the hippocampus [12] and the subventricular zone (SVZ) of the lateral ventricle [13]. Compounds that stimulate adult neurogenesis might protect against deterioration of brain functions,

most notably memory and learning capabilities, due to aging or adverse conditions. In this respect, it was reported that ginsenoside Rg1 increased the proliferating ability of neural progenitors both *in vitro* and *in vivo* under both physiological and pathological circumstances. For example, Shen and Zhang [14,15] found that ginsenoside Rg1 increased the number of proliferating progenitor cell spheres and the number of dividing cells in the hippocampus when incubated with neural proliferating cells and following intraperitoneal administration in adult mice. Cheng et al. [16] and Shen and Zhang [17] reported that ginsenoside Rg1 increased the extent of ischemia-induced proliferation and differentiation of neural progenitor cells in the dentate gyrus of the hippocampus in ischemic gerbils. The authors related this effect to nitric oxide (NO) and *N*-methyl-D-aspartate (NMDA) receptors as they found that ginsenoside Rg1 enhanced inducible nitric oxide synthase (iNOS) activity in the hippocampus of ischemic gerbils and systemic injection of MK-801, NMDA receptor antagonist, completely blocked the proliferating effect of ginsenoside Rg1. Liu et al. [18] found that ginsenoside Rg3 induced neurons in neural stem cells (NSCs). Blocking of such an effect with nifedipine, a Ca^{2+} channel antagonist, argues for involvement of voltage-dependent Ca^{2+} channel in ginsenoside Rg3-induced neurogenesis.

Ginsenosides Affect Neurotransmission

Neurotransmission is the process of neurotransmitter release from synapses where these compounds act on postsynaptic receptors on other neurons or cells in the CNS. Such processes are essential for propagation of signals from and to CNS via efferent and afferent neurons to further control smooth, skeletal and cardiac muscles, glandular secretions, and organ functions. Ginsenosides Rb1 and Rg1 have been reported to increase the release of the excitatory neurotransmitter glutamate in undifferentiated and differentiated PC12 cells [19]. The authors found that ginsenoside Rb1 promoted glutamate release by increasing phosphorylation of synapsins through cyclic adenosine monophosphate (cAMP)-dependent protein kinase (PKA). Synapsins are a family of proteins that are implicated to regulate neurotransmitter release at synapses. As a response of phosphorylation of synapsins, cytoskeleton-bound synaptic vesicles are released and move to the synaptic membrane and release their neurotransmitters into the synaptic cleft. Ginsenosides appear to enhance central cholinergic function. In this respect, Salim et al. [20] found that ginsenoside Rb1 increased the expression of choline acetyltransferase in the rat's basal forebrain, the enzyme that facilitates the formation of acetylcholine (ACh) via binding acetyl-CoA to choline. Benishin [21] reported that ginsenoside Rb1 boosted ACh release from hippocampal slices of rats. Moreover, ginseng total saponins (GTS) were found to increase the dopamine in the cerebral cortex, modulate dopaminergic activity at both presynaptic and postsynaptic receptors in mice [22,23], increase serotonin in rat cortices [24], raise the level of biogenic amines in normal rat brains [25], interact with nicotinic receptor subtypes [26] and regulate transmission of γ -aminobutyric acid (GABA) in animals [27,28]. Facilitating neurotransmitter release by ginsenosides may contribute to enhancing brain functions particularly learning, cognition, and memory.

Ginsenosides Support Memory and Learning

Cognitive deficits involving impairment of memory and learning are considered one of the most important consequences of aging [29]. Thus, searching for drugs that can prevent or even retard age-related cognitive deficits would be important for healthy aging. Ginsenosides were reported to improve cognitive function in aged animals and animal models of memory impairment. For instance, Wang et al. [30] reported that GTS facilitated learning and memory in normal Wistar rats. Wang et al. [30] and Yang et al. [31] found that ginsenoside Rh1 and Rh2 significantly ameliorated scopolamine-induced memory impairment and learning deficit in mice, respectively. They concluded that ginsenosides enhanced cognitive functions including memory and learning through targeting synapses. In this context, Wang and Zhang [32] reported that ginsenoside Rg1 enhanced the basic synaptic transmission and the magnitude of long-term potentiation (LTP) in the dentate gyrus of rats. Mook-Jung et al. [33] found that ginsenosides Rb1 and Rg1 increased hippocampal synaptic density as treated mice with ginsenosides contained higher density of a synaptic marker protein, synaptophysin, compared to control mice. Also, Zhao et al. [34] observed that a number of ginsenosides including Ra, Rb1, Rb2, Rc, Rd, Re, Rf, Rg1, Rg2, Rg3, and Ro were effective to prevent memory impairment by upregulating plasticity-related proteins in the hippocampus of 12 months old C57BL16 mice. Modulation of synaptic plasticity is considered one of the important molecular mechanisms of learning and memory.

Ginsenosides Affects and Regulate Ion Channels in Neurons

Neuronal ion channels are gated pores on cellular membranes. They are often selectively permeable to ions such as calcium (Ca^{2+}), potassium (K^{+}), or sodium (Na^{+}). The opening and closing of these channels are either voltage- or ligand-dependent.

Voltage-Dependent Ion Channels

Voltage-Dependent Ca^{2+} Channels

There are five different voltage-dependent Ca^{2+} channel subtypes such as L-, N-, P/Q- and T-type [35]. Excessive stimulation of voltage-dependent Ca^{2+} channels results in intracellular Ca^{2+} overload that leads to production of oxygen radicals and triggers the activation of various enzymes which are harmful to cells [36]. There is some evidence showing that ginsenosides can inhibit Ca^{2+} channels in neuronal cells. For example, Kim et al. [37] observed that GTS reduced KCl-induced neuronal loss in primary cortical neurons through inhibition of L-type Ca^{2+} channels. Similarly, Zhang et al. [38] found that ginsenoside Rg1 inhibited Ca^{2+} influx through L-type Ca^{2+} channels in primary hippocampal neurons.

Voltage-Dependent K^{+} Channels

Neurons like other cells have different types of K^{+} -selective ion channels including voltage-dependent, Ca^{2+} -activated,

ATP-sensitive, and G-protein-coupled inwardly rectifying (GIRK) channels. They are critical determinants of membrane excitability in neuronal cells as they set the resting membrane potential, oppose depolarization, and repolarize action potential [39]. Some ginsenosides were reported to regulate the electrical state of excitable neurons by activation of K^+ channels. For example, ginsenoside Rf activated GIRK channels through an unidentified G protein-coupled receptor in rat's brain [40].

Voltage-Dependent Na^+ Channels

Voltage-dependent Na^+ channels play a primary role in neuronal excitability and are critical target for neuromodulation [41]. There is some evidence on the regulation of neuronal Na^+ channels by ginsenosides. Kim et al. [42] reported that ginsenoside Rg3's carbohydrate component inhibited the inward Na^+ peak current in *Xenopus* oocytes. Lee et al. [43] observed that ginsenoside Rg3 inhibited Na^+ in *Xenopus* oocytes through acting on the resting and open states of Na^+ channel via interaction with the S4 voltage-sensor segment of domain II. Duan and Nicholson [44] reported that ginsenoside Rh2 inhibited veratridine-dependent depolarization (inhibition of Na^+ channel function) of mouse synaptoneurosomes with subsequent inhibition of release of l-glutamate and GABA. Liu et al. [45] reported that American ginseng (*Panax quinquefolius*) and ginsenoside Rb1 blocked ischemia-induced Na^+ fluxes in human embryonic kidney tsA201 cells through interaction with the inactive state of the channel.

Ligand-Dependent Ion Channels

The common ligand-dependent ion channels (ionotropic receptors) include NMDA-, nicotine acetylcholine-, and serotonin-gated ion channels.

NMDA-Gated Ion Channels

Activation of NMDA receptors by glutamate, the main excitatory neurotransmitter released extensively in neurological diseases and disorders such as Alzheimer disease (AD), ischemia, seizures, and trauma of head and neck, results in massive influx of Ca^{2+} into neurons. Intracellular Ca^{2+} overload is a key component of glutamate-mediated neurotoxicity [46]. Modulation of NMDA receptors by ginsenosides has been reported in some CNS disorders. For example, ginsenosides Rb1 and Rg3 have been reported to protect rat cortical and hippocampal neurons against glutamate- and NMDA-induced neurotoxicity, respectively, by deactivation of NMDA receptors [47,48]. Precisely, it was reported that ginsenosides inhibited NMDA receptors via interaction with different regulatory sites such as NMDA-, co-agonist glycine-, polyamine-binding sites, and sites within the lumen of the channel. In this context, Kim et al. [49] and Lee et al. [50] found that ginsenosides Rg3 and Rh2 selectively targeted NMDA receptor in primary hippocampal neurons via interaction with glycine- and polyamine-binding sites, respectively.

Nicotine Acetylcholine Ligand-Gated Ion Channels

Neuronal nicotinic receptors consist of α ($\alpha 2 - \alpha 9$) and β ($\beta 2 - \beta 4$) subunits. Activation of these receptors by ACh allows the influx of Na^+ into the cells. Various reports showed the ability of ginsenosides to regulate nicotine ACh receptor channels. Tachikawa et al. [51] reported that ginsenosides Rb1, Rb2, Rb3, Rc, Rd, Re, Rf, Rg1, Rh1, Ro, and Rs1 reduced ACh-evoked secretion of catecholamines from bovine adrenal chromaffin cells which contain mainly $\alpha 3\beta 4$ subunits of nicotinic receptors. Moreover, Choi et al. [52] found that ginsenosides Rg2, Rf, Re, Rg1, Rc, Rb2, and Rb1 inhibited acetylcholine-induced inward currents in *Xenopus* oocytes expressed with nicotinic receptors containing $\alpha 1\beta 1\delta \epsilon$ or $\alpha 3\beta 4$ subunits.

Serotonin-Gated Ion Channels

Among serotonin (5-hydroxytryptamine, 5-HT) receptors, activation of 5-HT₃ receptor renders it permeable to Na^+ and K^+ ions. Ginsenoside Rg2 and ginsenoside metabolites such as compound K and M4 were reported to inhibit the 5-HT₃ receptor-gated ion currents in *Xenopus* oocytes expressing 5-HT_{3A} receptors [53,54]. Lee et al. [55] connected the effect of ginsenosides on 5-HT receptors to the interaction with residues V291, F292, and I295 in the channel gating region of transmembrane domain 2 (TM2). The authors found that mutations of V291, F292, and I295 in the channel gating region of TM2 greatly attenuated or abolished ginsenoside Rg3-induced inhibition of peak I 5-HT.

Ginsenosides-Modulated CNS Targets Associated with neuroprotection

Parkinson Disease

Parkinson disease (PD) is a progressive neurodegenerative disease affecting 0.3% of the general populations worldwide. The main symptoms of PD are caused as the result of the progressive degeneration of the nigrostriatal dopaminergic pathway. Most of current therapies only provide symptomatic treatment and up till now, no drug has yet been found to prevent the progressive loss of dopaminergic neurons in PD patients [56]. Recently, it has been shown that ginseng and its active ingredients, ginsenosides, have beneficial effects on both *in vitro* and *in vivo* PD models. Ginsenosides, through involving antiapoptotic, antioxidant, and anti-inflammatory mechanisms, have been reported to protect nigrostriatal system in animal models. For example, Xu et al. [57] reported that ginsenoside Re rescued dopaminergic neurons in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mice through upregulating the expression of Bcl2 protein and down-regulating the expression of Bax and iNOS proteins and inhibiting activation of caspase-3. Chen et al. [58] found that attenuation of glutathione (GSH) reduction and the phosphorylation of JNK and C-Jun by ginsenoside Rg1 protected against MPTP-induced dopaminergic cell loss in C57-BL mice. Wang et al. [59] found that ginsenoside Rg1 rescued dopaminergic neurons in MPTP-treated mice through P38 signaling pathway that plays an important role in modulating cyclooxygenase-2 (COX-2) expression.

Moreover, Wang et al. [60] reported that ginsenoside Rg1 increased dopamine and its metabolites in the striatum and tyrosine hydroxylase (TH) expression in MPTP-treated mice by upregulating certain iron transporter proteins such as iron import protein, divalent metal transporter (DMT1) and iron export protein, ferroportin 1 (FP1). Elevated iron levels in substantia nigra (SN) may play a key role in the development of PD by enhancing the generation of oxidative stress [61,62]. Xu et al. [63] reported that activation of the insulin-like growth factor-1 (IGF-1) mediated the neuroprotective effects of ginsenoside Rg1 in 6-hydroxydopamine (6-OHDA)-treated rats. This neuroprotective effect of ginsenoside Rg1 was blocked by IGF-1 receptor antagonist, JB-1.

Similar to their effects on animal models, ginsenosides have been also found to protect *in vitro* cellular PD models through antiapoptotic, antioxidant, and anti-inflammatory mechanisms. For instance, it was reported that ginsenosides Rg1 attenuated rotenone-induced apoptosis in primary cultured rat nigral neurons by inhibiting the mitochondrial apoptotic pathway [64]. This effect of ginsenoside Rg1 was mediated by prevention of cytochrome *c* release from mitochondrial membrane and an increase in the inhibition of phosphorylation of the proapoptotic protein Bad through activation of the PI3K/Akt pathway. Also, the protective effect of ginsenoside Rg1 was blocked by glucocorticoid receptor (GR) antagonist RU486, indicating that the action of Rg1 is mediated through GR activation [64]. Regarding antioxidant activity, Ye et al. [65] concluded that ginsenoside Rd played a potent antioxidant role as it reduced intracellular reactive oxygen species (ROS) levels, decreased malondialdehyde (MDA) production, the common index of lipid peroxidation, and enhanced the antioxidant enzymatic activities of superoxide dismutase (SOD) and glutathione peroxidase (GPx) in hydrogen peroxide (H₂O₂)-treated PC12 cells. Against lipopolysaccharides (LPS)-induced neuroinflammation in primary dopaminergic cell culture, ginsenoside Rd was found to be effective through reduction of NO formation and PGE2 synthesis [66].

Alzheimer's Disease

Alzheimer's disease (AD), the most common cause of dementia in elderly people, has no cure so far. According to the current research, promising therapeutic strategies for AD include reduction of generation or aggregation of β amyloid peptide (β), enhancement removal of β from the cells, interruption of τ hyperphosphorylation and the use of more efficacious antioxidant and anti-inflammatory drugs. Ginsenosides have been recently reported to produce protective and trophic effects against AD. Yang et al. [67] reported that ginsenoside Rg3 significantly reduced the levels of β 40 and 42 in SK-N-SH cells transfected with Swedish mutant SweApp through enhancing neprilysin (NEP) gene expression, the rate-limiting enzyme in the β degradation in the brain. Moreover, ginsenoside Rg3 was found to promote β uptake, internalization and digestion by microglia in rat primary culture and this effect may be related to type A macrophage scavenging receptor (MSRA) expression [68].

There is large evidence indicating that phosphorylated τ plays a prominent role in the pathogenesis of AD [69]. Xie et al. [70] reported that pretreatment of hippocampal neurons with gin-

senoside Rb1 reduced hyperphosphorylation of τ protein induced by β 25–35. Chen et al. [71] found that ginsenoside Rb1 decreased τ phosphorylation in cortical neurons through inhibiting p35 expression, the cyclin-related activator molecule that regulates cyclin-dependent kinase-5 (CDK5) which, upon activation, results in τ phosphorylation.

Moreover, Shieh et al. [72] found that ginsenoside Rh2 could attenuate β -induced apoptosis in type I rat brain astrocytes through increasing expression of the neurotrophic factor, pituitary adenylate cyclase activating polypeptide (PACAP). Chen et al. [73] reported that ginsenoside Rg1 attenuated β 1–40-induced apoptosis in rat cortical neurons via inhibiting the activity of cyclin-dependent kinase-4 (CDK4), decreasing the phosphorylation of pRB and downregulation the expression of E2F1 mRNA. Wei et al. [74] found that ginsenoside Rg1 prevented Chinese hamster ovarian (CHO) tumor cells transfected with mutant PSIM146L gene from apoptosis through inhibiting the production of β 42 and decreasing the expression of the active caspase-3. Furthermore, it was found that ginsenosides did not only reduced β formation and β -induced hyperphosphorylation of τ and neuronal apoptosis but they also found to affect the activity of choline acetyltransferase and acetylcholinesterase. In parallel, Wang et al. [75] reported that ginsenoside Rg1 significantly ameliorated the learning and memory impairment induced by β -AP(25–35). The authors returned this effect of ginsenoside Rg1 to the prevention of cortical and hippocampal choline acetyltransferase activity decline and inhibition of the activity of acetylcholinesterase. It is of importance to know that central acting cholinesterase inhibitors are the first primary pharmacological treatment approved for AD.

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by degeneration of motoneurons in the spinal anterior horn [76]. Using mutant SOD1 transgenic mice (B6SJL-TgN(SOD-1G93A)1Gur), the relevant animal model for ALS, it was shown that crude ginseng powder significantly delayed the onset of signs of motor impairment and prolonged the survival of mice [77]. In this context, Kim et al. [78] reported that ginsenoside Rb2 significantly activated SOD1 gene through transcription factor AP2-binding site in human HepG2 hepatoma cells.

Huntington's Disease

Huntington's disease (HD) is an inherited progressive neurodegenerative disorder originated by the mutation of the gene encoding the huntingtin-protein (htt). The disease is characterized clinically by involuntary abnormal movements, cognitive deficits, and psychiatric disturbance and pathologically by degeneration of the GABAergic medium size spiny neurons [79]. In primary medium spiny striatal neuronal culture (MSN) from the YAC128 HD mouse, an *in vitro* model for HD, ginsenosides Rb1, Rc, and Rg5 protected cultured cells from glutamate-induced apoptosis through inhibiting glutamate-induced Ca²⁺ responses [80]. HD mutation affected Ca²⁺ signaling in MSN cultures by stimulating NR1/NR2B subunit of NMDA receptors [81]. Moreover, post-mortem tissue from HD patients showed reduced binding to

Table 1. Important ginsenosides' effects following activation of some CNS targets

Ginsenosides	CNS targets	Effects
Rg1	iNOS and NMDA receptor	Proliferation and differentiation of neuronal progenitor cells in dentate gyrus of the hippocampus in ischemic gerbils [16,17].
	Synapses	Increasing cognitive functions such as memory and learning through enhancing the basic synaptic transmission and the magnitude of LTP in the dentate gyrus of rats [32].
	L-type Ca ²⁺ channels	Inhibition of Ca ²⁺ influx into primary cultured hippocampal neurons [38].
	P38	Modulation of COX-2 expression with subsequent protection of dopaminergic neurons in MPTP-treated mice [59].
	DMT1 and FPI	Increasing dopamine and its metabolites in the striatum and TH expression in MPTP-treated mice [60].
	IGF-1	Protection of dopaminergic neurons in 6-OHDA-treated rats [63].
	GR	Restoring of $\Delta\Psi_m$, prevention the release of cytochrome c from mitochondrial membrane and increasing the phosphorylation inhibition of the pro-apoptotic protein Bad through activation of P13K/Akt pathways in rotenone-treated primary nigral cell culture [64].
Rg3	CDK4, pRB, and E2F1	Attenuation of A β -40-induced apoptosis in rat cortical neurons [73].
	Voltage-dependent Ca ²⁺ channels	Neuronal induction in neural stem cells (NSCs) [18].
	Glycine binding site of NMDA receptor	Protection of rat hippocampal neurons against NMDA-induced neurotoxicity [49].
	Neprilysin gene	Reduction the levels of A β 40 and 42 in SK-N-SH cells transfected with Swedish mutant SweApp [67].
Rg2	MSRA	Promotion of uptake, internalization and digestion of A β by microglia in rat primary culture [68].
	$\alpha 1\beta 1\delta\epsilon$ or $\alpha 3\beta 4$ subunits of NMDA receptor	Inhibition of acetylcholine-induced inward currents in <i>Xenopus</i> oocytes [52].
	V291, F292, and I295 residues of 5-HT _{3A} receptor channels	Inhibition of 5-HT ₃ receptor-gated ion currents in <i>Xenopus</i> oocytes [55].
Rb1	(cAMP)-dependent PKA	Phosphorylation of synapsins with subsequent release of glutamate in PC12 cells [19].
	Choline acetyltransferase	Formation of Ach in rat's basal forebrain [20].
	NMDA receptor	Protection of rat cortical neurons against glutamate neurotoxicity [47].
	$\alpha 3\beta 4$ subunits of nicotinic receptors	Reduction of Ach-evoked secretion of catecholamines from adrenal chromaffin cells [51].
	P35	Decreasing hyperphosphorylation of τ protein induced by A β 25–35 in cortical neurons [71].
Rb2	Transcription factor AP2 binding site	Activation of SOD1 gene in human HepG2 hepatoma cells [78].
Rf	Unidentified G protein coupled receptor	Activation of GIRK channels in rat's brain [40].
Rh2	Na ⁺ channels	Inhibition of L-glutamate and GABA release in mouse synaptoneurosome [44].
	Polyamine binding site of NMDA receptor	Protection of hippocampal neurons against glutamate and NMDA neurotoxicity [50].
	PACAP	Attenuation of A β -induced apoptosis in type I rat brain astrocytes [72].
	NF- κ B and MAP kinase	Inhibition of microglial activation in immortalized murine BV2 microglial cell line [98].
		Suppression of MMP-9 in PHA-treated astrogloma cells [100,101].
Re	Bcl2, Bax, iNOS. and caspase-3	Rescuing dopaminergic neurons in MPTP-treated mice [57].
Rd	iNOS and COX-2	Reduction of NO formation and PGE2 synthesis in LPS-treated dopaminergic neurons [66].
	GR	Reduction of neuronal death of primary rat hippocampal neurons induced by oxygen glucose deprivation [92].
PNS	ICAM-1	Attenuation of ischemic brain inflammation and inhibition of neutrophil infiltration [99].

glutamate receptors in the striatum [82,83] and decreased mRNA levels of the NR1 and NR2 subunits suggesting the loss of neurons containing NMDA receptors [84].

Brain Ischemia

Brain ischemia, the most important cause of chronic disability, is caused by low oxygen and glucose supply and a decrease in adenosine triphosphate (ATP) in the brain. Most of the recent studies support the role of oxidative mechanisms and energy depriving injuries in cerebral ischemia as the brain has low concentrations of oxygen radical scavenging enzymes and low fuel reserves, respectively [85]. Some ginsenosides have been reported to target different injurious factors in the ischemic cascade. For example, ginsenoside Rb1 was reported to prevent ischemic neuronal death in rats and protect ischemic CA1 neurons in gerbils through scavenging free radicals and increasing expression of antiapoptotic genes and modulating the expression of glial-derived neurotrophic factor (GDNF), respectively [86,87]. Moreover, ginsenosides Rb and RO protected against cerebral ischemia/reperfusion injury in rats by facilitating synthesis and release of prostacyclin in the brain and reducing formation of thromboxane A2 [88]. Also, ginsenosides Re and Rg3 were found to show neuroprotection against cerebral ischemia/reperfusion injury in rats by stabilizing mitochondria and enhancing the activities of SOD and GPx [89–91]. Similar to animal models, ginsenosides Rg1 and Rd reduced neuronal death of primary rat hippocampal neurons induced by oxygen glucose deprivation by activation of GR and inhibition of calcium influx through NMDA receptors and L-type voltage-dependent Ca^{2+} channels and by enhancing the antioxidant activities of catalase, SOD, and GPx, respectively [38,92].

Neuroinflammation

Following neural injury, microglia the resident immune cells of the CNS is activated and releases various neurotrophic factors such as BDNF, NT-3, and NGF. Upon over-activation, microglia releases neurotoxic factors, most notably NO and proinflammatory cytokines, which play an important role in the progression of neurodegenerative diseases such as AD and PD [93,94]. Ginseng extract and its saponins have been reported to protect neuronal cells against microglia-induced inflammatory processes. In this context, it has been reported that ginsenosides Rd, Rg1, Re, Rg3, and Rh2 reduced cytokines production by LPS- and $\text{A}\beta$ 42-stimulated microglial cells [66,95–97]. Using immortalized murine BV2 microglial cell line, Park et al. [98] found that inhibition of NF- κ B and MAP kinase, the upstream signaling inflammatory molecules, may be correlated with the anti-inflammatory effects of ginseng. Moreover, He and Zhu [99] reported that Panax notoginseng saponins (PNS) attenuated the ischemic brain inflammation

through decreasing expression of ICAM-1 and subsequent inhibition of neutrophil infiltration.

Brain Tumors

Among ginsenosides, ginsenoside Rh2 and compound K were reported to inhibit the *in vitro* invasiveness of astrogloma cells. Such effect was found to be mediated by inhibition of matrix metalloproteinase-9 (MMP-9), the enzyme that degrades extracellular matrix and consequently plays an important role in facilitating infiltration, migration, and invasion of gliomas [100,101]. Using PMA-treated astrogloma cells, the authors found that ginsenoside Rh2 and compound K, 20-O- β -(D-glucopyranosyl)-20(S)-protopanaxadiol derived from protopanaxadiol ginsenosides by intestinal bacteria, repressed the expression of MMP-9 through the inhibition of NF- κ B, AP-1 and P38MAPK, ERK, and JNK. Moreover, it was reported that ginsenoside Rh2 inhibited cell growth in MCF-7 human breast cancer cells and SK-HEP-1 hepatoma cells [102,103] and induced apoptosis in various cell lines including C6 rat glioma, SK-N-BE(2) C human neuroblastoma, and A375-S2 human malignant melanoma cells [104–106]. Also, Surh et al. [107] and Park et al. [108] observed that ginsenoside Rg3 inhibited the formation of PMA-induced mouse skin tumors.

The most important effects of ginsenosides Rg1, Rg3, Rg2, Rb1, Rb2, Rf, Rh2, Re and Rd on different CNS targets are summarized in Table 1.

Concluding Remarks

Ginseng's history can be divided into three eras. The first era was when the whole ginseng's roots were primarily used as a food by earlier Chinese. The second era was 2000 years later when ginseng was discovered to act as a tonic and adaptogen. The third one has begun since identification and isolation of ginsenosides in the middle of the last century. From that time, ginseng has been attracted much attention by researchers worldwide and hundreds of reports that described the beneficial effects of ginseng have been published worldwide. Most of these publications have been precisely described the mechanistic actions of different ginsenosides on various body systems using cellular and animal models. Obtained data are still not validated for patients against a particular disease due to shortage in clinical testing and validation. This review addressed the effect of the most common ginsenosides effects on different CNS targets and to try to prompt researchers in the future to analyze ginsenosides' actions using modern analytical tools particularly in clinical trials.

Conflicts of Interest

The authors declare no conflict of interests.

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