J Ginseng Res 43 (2019) 163–171

Contents lists available at ScienceDirect

Journal of Ginseng Research

journal homepage: http://www.ginsengres.org

Review Article

Emerging signals modulating potential of ginseng and its active compounds focusing on neurodegenerative diseases

Md. Jakaria [1], Joonsoo Kim [1], Govindarajan Karthivashan [2], Shin-Young Park [1], Palanivel Ganesan [2,3], Dong-Kug Choi [1,2,3,*]

[1] Department of Applied Life Science, Graduate School, Konkuk University, Chungju, Republic of Korea
[2] Research Institute of Inflammatory Disease, and Department of Biotechnology, College of Biomedical and Health Science, Konkuk University, Chungju 27478, Korea
[3] Nanotechnology Research Center, Konkuk University, Chungju, Republic of Korea

ARTICLE INFO

Article history:
Received 5 July 2017
Received in Revised form
8 January 2018
Accepted 12 January 2018
Available online 31 January 2018

Keywords:
Active compounds
Ginseng
Ion channels
Neurodegenerative diseases
Signaling pathway

ABSTRACT

Common features of neurodegenerative diseases (NDDs) include progressive dysfunctions and neuronal injuries leading to deterioration in normal brain functions. At present, ginseng is one of the most frequently used natural products. Its use has a long history as a cure for various diseases because its extracts and active compounds exhibit several pharmacological properties against several disorders. However, the pathophysiology of NDDs is not fully clear, but researchers have found that various ion channels and specific signaling pathways might have contributed to the disease pathogenesis. Apart from the different pharmacological potentials, ginseng and its active compounds modulate various ion channels and specific molecular signaling pathways related to the nervous system. Here, we discuss the signal modulating potential of ginseng and its active compounds mainly focusing on those relevant to NDDs.

1. Introduction

In the nervous system, neurodegenerative diseases (NDDs) are multifactorial debilitating disorders that are characterized by progressive dysfunction and neuronal injury leading to a slow but irreversible deterioration of brain functions which affects around 30 million individuals worldwide [1–4]. Although some symptomatic treatments are available, specific treatments have not yet been discovered [5]. Ginseng is considered to be one of the widely used traditional herbal medicines [6]. Ginseng and its constituents have been documented to produce aphrodisiac, adaptogenic, immunomodulatory, antiinflammatory, antioxidant, antiaging, anticancer, antifatigue, antidiabetic, pulmonary protective, hepatoprotective, cardioprotective, hypolipidemic, and renoprotective effects in various studies [7–21].

Furthermore, ginseng extracts and its active compounds have exhibited properties including antistress, antidepressive, and neuroprotective in various studies of neurological disease models [22–30]. They also enhanced cognitive performance and help maintain brain health [30–34]. Recently, various studies have reported on the potential role of ginseng and its active compounds in treating neurological disorders. Here, focusing on potential therapies for NDDs, we present the signal modulating potential of ginseng and its active compounds.

2. Role of ginseng and its active compounds in modulating ion channel signaling pathways

2.1. Modulation of voltage-gated ion channel

Various sources of evidence have suggested that ginsenosides regulate the neuronal Na^+ channels. In *Xenopus* oocytes, ginsenoside Rg3 carbohydrate component inhibited the inward Na^+ peak current [35]. Also, in *Xenopus* oocytes, Rg3 inhibited the Na^+ channel by acting on the resting and open states of the Na^+ channel via contact with the S4 voltage sensor segment of domain II [36]. Moreover, ginsenoside Rh2 inhibited the Na^+ channel function by inhibiting veratridine-dependent depolarization of mouse synaptoneurosomes following the inhibition of l-glutamate and γ-amino butyric acid releases [37].

* Corresponding author. Department of Biotechnology, College of Biomedical and Health Science, Konkuk University, Chungju 27478, Republic of Korea.
E-mail address: choidk@kku.ac.kr (D.-K. Choi).

https://doi.org/10.1016/j.jgr.2018.01.001
p1226-8453 e2093-4947/$ – see front matter

By activating the K^+ channel, some ginsenosides regulated the electrical state of excitable neurons. In *Xenopus* oocytes, ginsenoside Rg3 enhanced outward large-conductance Ca^{2+} and voltage-gated big K^+ (BK_{Ca}) channel currents in a concentration-dependent, voltage-dependent and reversible manner [38]. Moreover, in rat's brain, ginsenoside Rf–activated G protein-gated inwardly rectifying potassium (GIRK) channels through an unidentified G protein-coupled receptor [39].

In neuronal cells, ginsenosides are capable of inhibiting the Ca^{2+} channels. Ginseng total saponins are the main bioactive ingredients of *P. ginseng*. By inhibiting L-type Ca^{2+} channels, the ginseng total saponins decreased the KCl-induced neuronal loss in primary cortical neurons [40]. In *Xenopus* oocytes, BK_{Ca} channels are heterologously expressed. Gintonin treatment activated the BK_{Ca} channel and expressed the α-subunit of the BK_{Ca} channel in a concentration-dependent manner [41]. In primary hippocampal neurons, through L-type Ca^{2+} channels, ginsenoside Rg1 inhibited Ca^{2+} influx [42]. Furthermore, in the amyloid beta $(Aβ)_{25–35}$ model, ginsenoside Rg1 inhibits high-voltage–activated calcium channel currents in hippocampal neurons [43]. In addition, ginsenoside Rb1 inhibited voltage-gated calcium channel currents in a concentration-dependent manner, and upon washout, the current was mostly recovered. In hippocampal neurons, Rb1 selectively inhibits the action of L-type voltage-gated calcium channels without affecting the N-type or P/Q-type Ca^{2+} channels [44]. The signal modulating effects of active ginseng compounds on voltage-gated ion channels are shown in Fig. 1.

2.2. Modulation of the ligand-gated ion channel

2.2.1. Nicotinic acetylcholine receptors

Active ginseng compounds modulate nicotinic acetylcholine receptors (nAChRs). In oocytes expressing nAChR subunits (α1β1δε or α3β4), ginsenosides inhibited the acetylcholine (ACh)-induced inward currents (I_{ACh}). This potential indicates that ginsenosides directly control the nAChR channel activities. In the case of I_{ACh} inhibition, protopanaxatriol (PPT) ginsenosides (Re, Rf, Rg1, or Rg2) were more powerful than protopanaxadiol (PPD) ginsenosides including Rb1, Rb2, Rc, and Rd [45]. Conversely, by the desensitization of ACh induced in oocytes expression, ginsenoside Rg2 reduced the peak current and elevated the inward currents in human nAChR subunits α3β4, α3β2, α4β4, and α4β2 [46]. Moreover, through nAChR channel activity, ginsenosides show the inhibitory effects on I_{ACh} reduction of catecholamine release. Regarding the heterologous expression of the α9α10 subunits of nAChR in *Xenopus* oocytes, I_{ACh} is blocked by ginsenosides with a potency order of Rg3 > Rb2 > CK > Re = Rg2 > Rf > Rc > Rb1 > Rg1 in a rescindable means. Ginsenoside Rg3's blocking effects on I_{ACh} were the same after preapplication linked to ginsenoside Rg3 co-application. Furthermore, α10 subunit of α9α10 nAChR might play an important role in Rg3-induced regulation of the α9α10 nAChR [47]. Besides, a recent study described the ameliorative effect of Rg1 on lipopolysaccharide (LPS)-induced cognitive deficits. Rg1 treatment inhibited LPS-induced reduction of ACh levels and an increase in acetylcholinesterase activity. LPS treatment reduced the α7 nAChR protein expression in the prefrontal cortex and hippocampus, but Rg1 treatment reverted the changes [48]. Furthermore, choline acetyltransferase (ChAT) and vesicular acetylcholine transporter (VAChT) are essential for cholinergic neurotransmission. Ginsenosides Rd and Re regulated both ChAT and VAChT. In Neuro-2a cells, the Rd and Re effectively induced the ChAT/VAChT genes expression and ACh promotion [49].

2.2.2. γ-amino butyric acid receptors

Ginsenosides interact with the γ-amino butyric acid ($GABA_A$) receptor and might regulate the ligand binding with the $GABA_A$ receptor. In a rat brain membrane fraction, ginsenosides differentially regulate the binding of $[^3H]$-flunitrazepam or $[^3H]$-muscimol to the $GABA_A$ receptor [50]. Conversely, longer infusion of ginsenoside Rc raises $[^3H]$-muscimol binding to the $GABA_A$ receptor in a region-specific way in the rat brain [51]. Another study showed that ginsenosides enhance the GABA-mediated channel activity and thus control the $GABA_A$ receptor channel activity [52]. Therefore, in studies using *Xenopus* oocytes, ginsenosides Rb1, Rb2, Rc, Rd, Re, Rf, Rg1, and Rg2 affected the activity of $GABA_A$ receptor channel in human recombinant $GABA_A$ receptor expression. Ginsenoside Rc utmost potently improved the GABA-induced inward peak current (I_{GABA}). A $GABA_A$ receptor antagonist (bicuculline) and a $GABA_A$ channel blocker (picrotoxin) blocked the ginsenoside Rc stimulatory effect on I_{GABA}. Regarding the Cl^- channel blockers, niflumic acid and, on the I_{GABA}, 4,4′-diisothiocyanostilbene-2,2′-disulfonic acid both attenuated the ginsenoside Rc effect. Therefore, by affecting the binding affinities of the $GABA_A$ receptor ligands, ginsenosides may regulate the $GABA_A$ receptor [52]. Besides, the

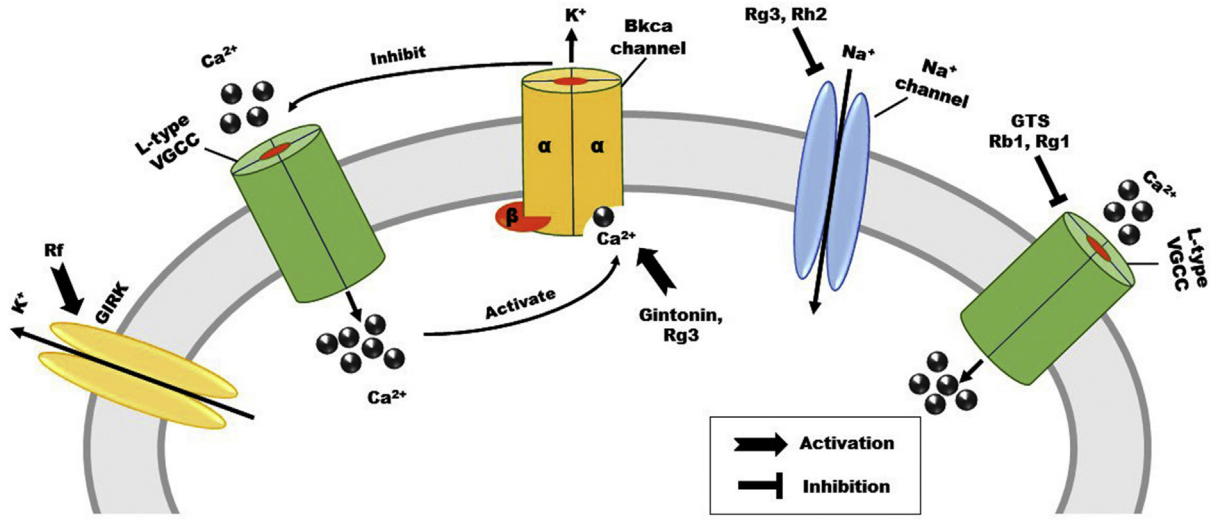

Fig. 1. Effects of active ginseng compounds on voltage-gated ion channels. Active ginseng compounds modulate the channels activities. GTS, ginseng total saponins; GIRK, G protein-gated inwardly rectifying potassium; L-type VGCC, L-type voltage-gated calcium channel; BKca channel, large-conductance Ca^{2+} and voltage-gated big K^+ channel.

regulatory effects of ginsenoside metabolites differ from those of ginsenosides. The human recombinant $GABA_A$ receptor ($\alpha_1\beta_1\gamma_{2s}$) channel activity expressed in *Xenopus* oocytes, M4, a metabolite of PPT ginsenosides, more potently inhibited the I_{GABA} than PPD. The effect of M4 and PPD on I_{GABA} was both concentration-dependent and reversible. The half-inhibitory concentration (IC_{50}) values of M4 and PPD were 17.1 ± 2.2 and 23.1 ± 8.6 μM, respectively. The inhibition of I_{GABA} by M4 and PPD was voltage-independent and noncompetitive [53]. Using a conventional whole-cell patch-clamp technique in acutely isolated rat hippocampal CA3 pyramidal neurons, compound K produced a potential effect on GABAergic spontaneous miniature inhibitory postsynaptic currents. Compound K increases spontaneous GABA release by increasing intraterminal Ca^{2+} concentration through Ca^{2+} release from presynaptic Ca^{2+} stores [54]. A recent report indicated that $GABA_A$ receptor agonist pretreatment significantly potentiated the *Panax quinquefolius* neuroprotective effect. Regarding the sleep deprivation, GABAergic mechanism induced anxiety-like behavior, mitochondrial dysfunction, oxidative stress, hypothalamic–pituitary–adrenal axis activation and neuroinflammation that could be involved in the *P. quinquefolius* neuroprotective outcome [55].

2.2.3. Glutamate receptors channel activity

In different neurotoxic agents–induced models, active ginseng compounds produced effects that confirmed the potential effects of ginseng active compounds on glutamate receptors. In rat hippocampal cultures, Rg3 reduced the high K^+-, glutamate-, and N-methyl-D-aspartate (NMDA)-induced Ca^{2+} influx [56]. Ginseng total saponins decreased glutamate-induced cultured rat astrocytes swelling [57]. Ginsenosides Rb1 and Rg3 produced a protective effect against glutamate-induced neurotoxicity. In this study, Rb1 and Rg3 prevent the nitric oxide (NO) overproduction, malondialdehyde formation. The treatments also preserved the superoxidase dismutase level and diminished the Ca^{2+} influx in rat cortical cultures [58]. In the Huntington's disease model, the neuroprotective effects of ginsenosides Rb1, Rc, and Rg5 might be due to the inhibition of glutamate-induced Ca^{2+} responses in cultured medium spiny striatal neuronal culture [59]. In cultured mouse cortical neurons, notoginsenoside R1 (NGR1) also prevented glutamate-mediated neurotoxicity [60]. Pretreatment with ginsenosides attenuated NMDA- or substance P-induced nociceptive behavior through the intrathecal route [61,62]. With respect to the ginsenosides, the pretreatment attenuates the kainate-induced cellular death in hippocampal neurons [63]. Ginsenoside Rb3 could exert a neuroprotective role on hippocampal neurons, a role which was partly mediated by the facilitating Ca^{2+}-dependent deactivation of NMDA receptors and the resulting reduction of intracellular free Ca^{2+} level [64]. Ginsenosides Rh2 and Rg3 prevent the NMDA receptor channel currents in cultured rat hippocampal neurons [65]. Moreover, in *in vitro* and *in vivo* studies of homocysteine (HC)-induced hippocampal excitotoxicity, ginsenoside Rg3 produced neuroprotective activity. Furthermore, *in vivo* experiments showed that intracerebroventricular Rg3 preadministration significantly and dose-dependently decreased the HC-induced hippocampal damage in rats. Treatment with Rg3 has been found to dose-dependently inhibit the HC-induced elevation of intracellular Ca^{2+} levels. In addition, in *Xenopus* oocytes expressing the NMDA receptor, Rg3 treatment dose-dependently repressed HC-induced currents [66]. Regarding the effects of ginsenoside metabolites on NMDA receptor channel activity, PPT contrasting compound K and PPD were reversibly repressed the NMDA-mediated inward currents (I_{NMDA}) in a dose-dependent manner. I_{NMDA} inhibition by PPT was noncompetitive with NMDA and was self-regulating the membrane holding potential, although ginsenoside Rh2, Rg3, and PPT interrelate with the NMDA receptor [67]. Ginsenoside Rb1 produced the anti-fatigue effect through the inflammatory cytokine-mediated NMDA receptor pathway [68]. The protective effects of active ginseng compounds on toxins-induced excitotoxicity through the glutamate receptors are shown in Fig. 2.

3. Various specific molecular signaling and their modulating effect by ginseng and its active compounds

3.1. Toll-like receptor involving pathways

In an Alzheimer's disease (AD) cellular model, ginsenoside Rg1 produced antineuroinflammatory activity through a toll-like receptor (TLR) pathway. In NG108-15 cells, $A\beta_{25-35}$ markedly

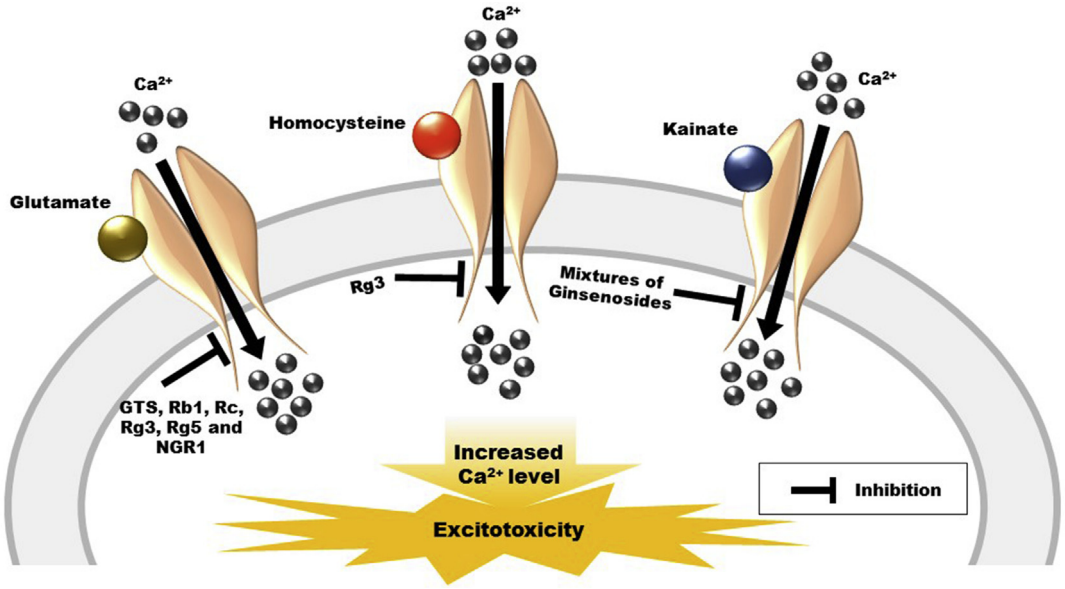

Fig. 2. Potential activities of active ginseng compounds in toxin-induced neurotoxicity models. GTS, ginseng total saponins; NGR1, notoginsenoside R1. Glutamate, homocysteine and kainate cause an increase in intracellular calcium level leading to excitotoxicity. Active ginseng compounds produce protective activities against toxins-induced excitotoxicity.

increased the expressions of TLR3 and TLR4. In a concentration-dependent manner, Rg1 significantly reduced the expressions of both proteins as well as mRNA of TLR3 and TLR4 [69].

3.1.1. Mitogen-activated protein kinase pathway

Red ginseng marc oil (RMO) reduced the p38 mitogen-activated protein kinase (MAPK) and its upstream kinases including MAPK kinases 3/6 (MKK3/6) phosphorylation. By blocking the p38 MAPK pathway, RMO produced an antiinflammatory effect in LPS-induced RAW 264.7 macrophages [70]. Ginseng pectin pretreatment enhanced the phosphorylation of both the extracellular signal-regulated kinases 1 and 2 (ERK1/2) in cortical neuron cells and in U87 cells, it also increased the ERK1/2 phosphorylation. Owing to the activation of the phosphorylation of ERK1/2, ginseng pectin produced this neuroprotective activity against H_2O_2-induced apoptosis [71]. In LPS-induced RAW 264.7 cells, synthesized gold nanoparticles (AuNPs) using *Panax ginseng* exert antiinflammatory effects through p38 MAPK [72]. Likewise, gintonin produced antiinflammatory activity via the signal transduction through MAPK, and it potently suppressed the NO production and also efficiently suppressed the proinflammatory cytokines levels in RAW 264.7 cells [73].

Different doses of ginsenoside Rb1 pretreatment noticeably attenuated tau protein hyperphosphorylation and the expression of c-Jun N-terminal kinase (JNK)/p38 MAPK in $A\beta_{25\text{-}35}$-induced model [74]. In 1-methyl-4-phenylpyridinium (MPP^+)-treated PC12 cells, Rb1 improved ERK1/2 phosphorylation and reduced phosphorylated p38 or stress activated protein kinase/JNK. Rb1 increased ERK1/2 phosphorylation, and it was abrogated by estrogen receptor siRNA [75]. By upregulating the growth-associated protein 43 (GAP-43) expression through ERK-dependent signaling pathways, ginsenoside Rd may help PC12 cells neurite outgrowth [76]. In addition, Rd efficiently inhibited the activation of the MAPK signaling pathway induced by spinal cord injury in the rat model, which might be involved in the neuroprotective activity of Rd against spinal cord injury [77].

In various studies, ginsenosides Rg1 and Rg5 have shown potential effects through this pathway. To promote cell proliferation, ginseng and Rg1 increase the MAPK signaling pathways. In RSC96 cells, ginseng and Rg1 were recognized to have proliferative effects that are MAPK signaling-dependent [78]. In addition, Rg1 produced antiinflammatory activity in BV-2 microglial cells. In this study, phosphoinositide phospholipase C-γ1 inhibition was moderately abolished, and Rg1 produced an inhibitory effect on ERK1/2, JNK, and p38 MAPK phosphorylation. Therefore, by suppressing the neurotoxic proinflammatory mediators and cytokines expression, Rg1 expressively attenuates the overactivation of microglial cells through phospholipase C-γ1 signaling pathway activation [79]. Besides, Rg1 improves the neurite outgrowth and defends against $A\beta_{25-35}$-induced damage, and this mechanism may be involved in the activation of ERK1/2 signaling [80]. Additionally, Rg1 activated the ERK/MAPK pathway in another study [81]. Ginsenoside Rg5 inhibited the phosphorylation of MAPKs and the DNA binding activities in LPS-stimulated BV-2 microglial cells and primary rat microglia [82].

NGR1 and compound K show potential activity through the modulation of this pathway. NGR1 produces a sufficient effect by inducing an estrogen receptor–dependent ERK1/2 pathway [83]. Compound K significantly suppressed the Phorbol-12-myristate-13-acetate-mediated p38 MAPK, ERK, and JNK activation, which are upstream modulators of activator protein-1. In addition, compound K also inhibited the invasiveness of *in vitro* glioma cells [84].

3.1.2. Nuclear factor kappa-light-chain-enhancer of activated B cells pathway

RMO and AuNPs obtained from the leaf extract of *P. ginseng* and gintonin produced antiinflammatory activities in the LPS-induced RAW 264.7 macrophage cell line [70,72,73]. RMO treatment reduced the inducible nitric oxide species and cyclooxygenase-2 at both the mRNA and protein levels, with a blockade of the nuclear translocation of the p65 subunit. Hence, due to the inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) transcriptional activity, RMO might produce this antiinflammatory effect [70]. Moreover, AuNPs decreased inflammatory mediators, including NO, prostaglandin E2, interleukin-6, and tumor necrosis factor-α, expression. In RAW 264.7 cells, AuNPs suppressed the LPS-induced activation of NF-κB signaling [72]. At the given doses, gintonin effectively suppressed the NO production without any cytotoxicity and also proficiently suppressed the proinflammatory cytokines levels. Furthermore, it facilitates signal transduction through NF-κB pathways and recovers the mir-34a and mir-93 levels [73].

In the AD model, *P.* ginseng ginsenosides Rg1, Rg3, Rd, and Rg3 enriched the extract, producing potential activities [85–88]. In an advanced glycation end product–induced AD model, *ginseng* showed the neuroprotective effects through the significant decrease in the expression of the receptor for advanced glycation end-products and NF-κB in a rat [86]. In transgenic mice, Rd might improve learning and memory ability in used Aβ precursor by inhibiting the transcription activity of NF-κB. Moreover, by suppressing the activated NF-κB pathway, the proinflammatory cytokines were further reduced, and the protective factors were generated [87]. In a scopolamine-induced model, the oral administration of ginsenoside Rg3-enriched ginseng extract (Rg3GE) suppressed the increase in acetylcholinesterase activity and stimulation of the NF-κB pathway (i.e., phosphorylation of p65) in the hippocampus [88]. In the LPS-induced BV-2 microglia cell line, ginsenosides Re and Rh1 produced antiinflammatory activity [89,90]. Re produced neuroprotective events through phospho-p38, iNOS, and COX-2 signaling pathways [89]. Without affecting NF-κB DNA binding, ginsenoside Rh1 inhibited LPS-induced NF-κB–mediated transcription. In addition, an increase in cAMP responsive element-binding protein was identified to result in the suppression of NF-κB–mediated transcription [90]. Moreover, in a study of oxidative stress, ginsenoside Rg1 normalized the oxidative stress–induced nonmuscle myosin heavy chain IIA (NMMCH IIA) overexpression in PC12 cells. The collected data showed that the NMMCH IIA-NF-kappa B/p65 pathway was involved in oxidative stress–induced cell death [91]. The effects of active ginseng compounds through the MAPK and NF-κB pathways are summarized in Table 1.

3.2. Caspase-3 and Bcl-2-like protein 4-mediated pathways

Ginsenosides showed potential activity through these pathways. NGR1 produced neuroprotective activity by suppressing caspase-3 activation [83]. In PC12 cells, ginsenoside Rb1 prevented MPP^+-induced caspase-3 activation and DNA fragmentation. Besides, Rb1 also activated B-cell lymphoma-extra-large (Bcl-xL) and reduced apoptosis [75]. Ginsenoside Rg1 inhibited the caspase-3 signaling pathway and myosin IIA-actin interaction, and through these inhibitions, it produced neuroprotective activity [92]. In an MPP^+-induced apoptosis in human neuroblastoma (SH-SY5Y) cells model, Rg1 can effectively decrease the expression of MPP^+-induced upregulation of Bax and decrease the B-cell lymphoma 2 (Bcl-2) expressions. In addition, Rg1 can effectively decrease the MPP^+-induced toxicity by inhibiting the activation of caspase-3 [93]. A recent study revealed that ginsenoside Rd prevented trimethyltin-induced cell apoptosis via regulation of caspase-3, Bcl-2, and Bcl-2–like protein 4 [94]. With respect to the ginsenoside Rb1, it suppressed the activation of ER stress-associated proteins including protein kinase RNA–like endoplasmic reticulum kinase

and C/EBP homology protein and high glucose induced Bcl-2 downregulation in hippocampal neurons [95].

3.3. Phosphoinositide 3-kinase/protein kinase B pathway

Ginseng protein produced neuroprotective activity in D-galactose/AlCl3-induced AD model, and protective effect is connected to the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) signaling pathway [96]. Ginseng protein decreased the $A\beta_{1-42}$ content and phosphor-tau and enhanced the mRNA and PI3K and phospho-Akt/Akt protein expression in the hippocampus [96]. Ginsenoside Rd promotes the glutamate clearance, which was achieved by upregulating the glutamate transporter 1 expression via the PI3K/Akt pathway [97]. Neurite outgrowth is a crucial process associated with neuronal repair. In addition, Rd produced an effect on neurite outgrowth, and the upregulation of GAP-43 expressions through PI3K/Akt-dependent pathways might be responsible for this activity [76]. Furthermore, an experimental Parkinson's disease model induced by MPP^+ in SH-SY5Y showed that different concentrations of Rd had a neuroprotective effect. This protective effect might be due to the PI3K/Akt survival-signaling pathway [98].

Various studies have shown that ginsenosides Rg1 and Rg5 show beneficial effects through this pathway. Ginsenoside Rg1 enhances

Table 1
Potential effects of ginseng and its active compounds through the MAPK and NF-κB pathways.

Ginseng/active compounds	Models	Major effects	References
Rb1	$A\beta_{25-35}$-induced embryo rat cortical neurons	Different doses attenuate tau protein hyperphosphorylation and the expression of JNK/p38 MAPK in the process.	[74]
	MPP^+-treated PC12 cells	Improves ERK1/2 phosphorylation levels and reduced phosphorylated p38 or SAPK/JNK.	[75]
Rd	PC12 cells	Helps the neurite outgrowth through upregulating the growth associated protein 43 expression through ERK-dependent signaling pathways.	[76]
	Spinal cord injury in rat	Produces neuroprotective activity by efficiently inhibiting the activation of the MAPK signaling pathway.	[77]
	APP transgenic mice	By inhibiting the transcription activity of NF-κB, might improve learning and memory when APP is used. Moreover, by suppressing the activated NF-κB pathway, further reduces the pro-inflammatory cytokines and generates protective factors.	[87]
Rg1	$A\beta_{25-35}$-induced NG108-15 cells	Reduces the increased expressions of both TLR3 and TLR4.	[69]
	RSC96 cells	Produces the proliferative effects through the MAPK signaling−dependent pathway.	[78]
	BV-2 microglial cells	Attenuates the overactivation of phosphoinositide phospholipase C-γ1 and produces the inhibitory effect on the ERK1/2, JNK and p38 MAPK phosphorylation.	[79]
	$A\beta_{25-35}$-induced cultured hippocampal neurons	Improves neurite outgrowth and defends against damage, and the mechanism may comprise the activation of ERK1/2 signaling.	[80]
	PC12 cells	By CaMKIIα, it activates the ERK/MAPK pathway.	[81]
	H_2O_2-induced PC12 cells	Normalizes the oxidative stress-induced NMMCH IIA overexpression. Regarding the collected data, NMMHC IIA-NF-kappa B/p65 pathway involved in oxidative stress-induced cell death.	[91]
Rg3GE	Scopolamine-induced mice	Suppresses the increase in acetylcholinesterase activity and stimulation of the NF-κB pathway (i.e., phosphorylation of p65) in the hippocampus.	[88]
Rg5	LPS-stimulated BV-2 microglial cells and rat primary microglia	Inhibits the phosphorylation of MAPKs and the DNA binding activities.	[82]
Rh1	LPS-induced microglia	Without affecting NF-κB DNA binding, it inhibits NF-κB−mediated transcription. In addition, due to the NF-κB−mediated transcription, an increase of cAMP responsive element-binding protein might have been identified.	[90]
Re	LPS-induced BV-2 microglia	Produces the neuroprotective events through the phospho-p38, iNOS and COX-2 signaling pathways.	[89]
RMO	LPS-induced RAW 264.7 macrophages	Reduces the p38 MAPK and its upstream kinases including MAPK kinases 3/6 (MKK3/6) phosphorylation.	[70]
	LPS-induced RAW 264.7 macrophages	Reduces the iNOS and COX-2 at both mRNA and protein levels, blockade of nuclear translocation of the p65 subunit. Henceforth, due to the inhibition of NF-κB transcriptional activity, it might have produced this anti-inflammatory effect.	[70]
Ginseng Pectin	H_2O_2-induced apoptosis in cortical neuron cells and U87 cells	Pretreatment enhances the phosphorylation of both the extracellular signal-regulated kinases 1 and 2 (ERK1/2).	[71]
AuNPs	LPS-induced RAW 264.7 cells	Exerts anti-inflammatory effects through the suppression of NF-κB signaling pathway activation through p38 MAPK.	[72]
	LPS-induced RAW 264.7 cells	Decreases inflammatory mediators such as NO, prostaglandin E2, interleukin-6 and tumor necrosis factor-α, expression.	[72]
Gintonin	LPS-induced RAW 264.7 cells	Produces anti-inflammatory activity via the signal transduction through MAPK, and potently suppresses the nitric oxide production and also efficiently suppressed the proinflammatory cytokines levels.	[73]
	LPS-induced RAW 264.7	Effectively suppresses the NO production without any cytotoxicity and also proficiently suppresses the proinflammatory cytokines levels. Furthermore, facilitates signal transduction through NF-κB pathways and recovers the mir-34a and mir-93 levels.	[73]
NGR1	H_2O_2-induced PC12 cells	Produces neuroprotective activity the effect by inducing an estrogen receptor-dependent ERK1/2 pathway.	[83]
Compound K	Phorbol myristate acetate−mediated human astroglioma cells	Significantly suppresses the p38 MAPK, ERK, and JNK activation, which are upstream modulators of activator protein-1.	[84]
Ginseng	Advanced glycation end product− induced AD in rat	Shows neuroprotective effects through the significant decreasing the expression of receptor for advanced glycation end-products and NF-κB.	[86]

AD, Alzheimer's disease; APP, amyloid β-protein precursor; AuNPs, synthesized gold nanoparticles; CaMKIIα, calcium/calmodulin-dependent protein kinase type II alpha chain; JNK, c-Jun N-terminal kinase; LPS, lypopolysaccharide; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated; NGR1: notoginsenoside R1; NMMCH IIA, nonmuscle myosin heavy chain IIA; NO, nitric oxide; Rg3GE, Rg3-enriched ginseng extract; RMO, Red ginseng marc oil; SAPK, stress activated protein kinase; TLR, toll-like receptor.

neurite outgrowth and protects against $A\beta_{25-35}$-induced damage, and its mechanism may involve the activation of Akt signaling [71]. In LPS-stimulated BV-2 microglial cells and rat primary microglia, Rg5 produced an antiinflammatory activity. The studies indicated that Rg5 inhibited the phosphorylation of PI3K which are upstream molecules controlling the inflammatory reactions [82]. Moreover, pseudoginsenoside-F11 produced antineuroinflammatory activity on activated microglia. Pseudoginsenoside-F11 inhibited neuroinflammation LPS-induced in N9 microglia by inhibiting the activation of TLR4 mediated PI3K/Akt pathways [99]. NGR1 produced a neuroprotective activity by suppressing the H_2O_2-induced intracellular reactive oxygen species accumulation and increasing the product of lipid peroxidation (malondialdehyde), protein oxidation (protein carbonyl), DNA fragmentation (8-OHdG), mitochondrial membrane depolarization as well as caspase-3 activation. This neuroprotective activity is occurred by inducing estrogen receptor-dependent crosstalk between Akt pathways [83].

3.4. Insulin-like growth factor-I receptor signaling

A study of MPP^+-induced apoptosis model in PC12 cells showed that ginsenoside Rb1 had neuroprotective effects. In caspase-3-dependent apoptosis pathway, Rb1 protects the PC12 cells through the estrogen receptor [75]. In a study on RSC96 Schwann cells, ginseng and ginsenoside Rg1 exhibited proliferation and migration-enhancing properties. Ginseng and ginsenoside Rg1 improve the insulin-like growth factor-I receptor (IGF-IR) pathway regulators' protein expression. Moreover, Rg1 with biomedical materials would be a possible method to improve neuron regeneration [78]. Ginsenoside Rg1 produced neuroprotective effects against 6-hydroxydopamine (6-OHDA)–induced neurotoxicity [100,101]. In the 6-OHDA–induced model of nigrostriatal injury, Rg1 showed a neuroprotective activity, and this effect might involve the activation of the IGF-IR signaling pathway. Rg1 treatment ameliorated this behavior in apomorphine-induced rotational behavior. In addition, 6-OHDA significantly reduced the striatum dopamine content, and Rg1 reversed the significant effects of 6-OHDA [101]. Besides, in 6-OHDA–induced neuronal damages in SK-N-SH cells, Rg1 produced neuroprotective effects through the activation of the IGF-IR, ER signaling pathways, and its antiapoptotic potentials [100].

3.5. Nuclear factor (erythroid-derived 2)-like-2 factor pathway

P. ginseng extract produced antidepressant activity in a chronic restraint stress -induced depression model in mice. In this study, *P. ginseng* extract showed anti-neuroinflammatory and antioxidant, nuclear factor (erythroid-derived 2)-like-2 factor/heme oxygenase-1 (Nrf2/HO-1 activation) activity by inhibiting the hypothalamo–pituitary–adrenal axis mechanism [102]. Ginsenoside Rb1 activates the Nrf2/HO-1 signaling pathway to display a potent neuroprotective activity against tert-butylhydroperoxide–induced oxidative injury. In cultured neural progenitor cells, Rb1 activates the Nrf2 pathway and led to an elevated HO-1 expression [103,104]. In iron-induced neurotoxicity, the antioxidative properties that trigger the Akt/Nrf2 pathway and increase the Nrf2-induced HO-1 and Cu/Zn superoxidase dismutase expression allowed ginsenoside Rg1 protect the human neuroblastoma SK-N-SH cells [105]. Similarly, ginsenoside Rh3 improves the Nrf2 DNA-binding activity [106]. PPT ginsenosides improve the Nrf2 inflowing to the nucleus and induced antioxidant response elements (ARE) such as HO-1 and the expression of nicotinamide adenine dinucleotide phosphate (NADPH) quinone oxidase 1. Subsequently, PPT shows a neuroprotective activity against 3-nitropropionic acid–induced injury (oxidative stress) in the rat model of Huntington's disease [107]. Additionally, NGR1 improves Nrf2 nuclear translocation and ARE activity. It also upregulates the expression and effects of HO-1, NADPH quinone oxidase 1, and gamma-glutamylcysteine synthetase. NGR1 provides neuroprotective activity by inducing the estrogen receptor-dependent activating Nrf2/ARE signaling [83].

3.6. Nerve growth factor and brain-derived neurotrophic factor pathways

Various research studies have shown that ginseng extracts, as well as its active compounds, exert potential activity through these pathways. In Neuro-2a cells, ginsenosides Rd and Re treatments meaningfully improved the microtubule-associated protein-2, nerve growth factor receptor (p75), p21, and tropomyosin receptor kinase A genes and proteins expression. Therefore, Re and Rd play a significant role in differentiation of neuron and the nerve growth factor–tropomyosin receptor kinase A signaling pathway [49].

In the rat model, *P. ginseng* showed neuroprotective activity against LPS-induced brain injury. LPS causes elevated brain NO and serum HC associated with a reduction of brain-derived neurotrophic factor (BDNF) level. On the other hand, in the treated group, *P. ginseng* significantly attenuated these compared to the LPS group [108]. A study showed that *P. notoginseng* saponins promote the rat embryonic cortical neural stem cells survival, self-renewal, proliferation, and differentiation through neurotrophic factors in the autocrine or paracrine signaling [109].

Ginsenoside Rg1 also improved the memory performance [110,111]. In the AD model, Rg1 treatment reduced the $A\beta_{1-42}$ accumulations and phosphorylated (p)-Tau protein. Rg1 treatment also upregulated the BDNF and phosphorylated tropomyosin receptor kinase B. Similarly, Rg1 treatment also restored the long-term potentiation in the AD mice model. In another study, through the hippocampal BDNF upregulation, Rg1 treatment improved the memory performance in middle-aged mice, changing apical spines and helping hippocampal long-term potentiation [111].

Ginsenoside Rb1 revealed a neuroprotective activity against cerebral ischemia. After Rb1 infusion, the number of nestin-positive cells apparently increased. At different points in time, Rb1-treated rats showed a BDNF level that significantly improved compared to that of ischemic rats. These neuroprotective effects might be because of the promotion of the neurogenesis and expression of BDNF regulation [112]. In addition, Rb1 showed the preventive and therapeutic effects on the neural injury during cerebral infarction in rat's model via middle cerebral artery occlusion. The increases in occlusion duration resulted in a decline in interleukin-1 levels and GAP-43 level and an increase in BDNF levels and neurofilaments. These effects might be due to a decrease in inflammation and assistance in the growth of nerve cells [113].

Ginsenosides Rb3, Rg1, and Rg3 produced antidepressant activity through the BDNF signaling pathway [114–117]. In a study of the chronic mild stress model, treatment with Rb3 significantly increased the BDNF level in the prefrontal cortex and hippocampus area [114]. Rg1 produced antidepressant activity via BDNF signaling pathway. It upregulates the BDNF expression and hippocampal neurogenesis [115,116]. Recently, Rg1 treatment prevented chronic social defeat stress–induced depressive-like symptoms in a depression-induced mouse model [116]. Furthermore, Rg3 completely restored the chronic social defeat stress–induced reduction in the hippocampal BDNF signaling pathway [117].

3.7. Mechanistic target of rapamycin signaling, Wnt/β-catein and Rho-associated kinase 1/Myosin light-chain kinase pathways

Compound K is produced potential activity through the mechanistic target of rapamycin pathway. In a study of AD model, compound K promotes Aβ clearance and enhances autophagy in

primary astrocytes. It also slows AD pathological progression. In addition, due to the mechanistic target of rapamycin phosphorylation, it might contribute to an enhancement in the autophagy [118]. In *in vivo* and *in vitro* Parkinson's disease models, ginsenoside Rg1 showed neuroprotective potentials through the Wnt/β-catenin signaling pathway. In both the *in vivo* and *in vitro* studies, Rg1 showed protective effects on the protein and mRNA expression levels of this pathway marker. With respect to the *in vitro* study, the neuroprotective potentials were blocked by Dickkopf-related protein 1 [119]. In a H_2O_2-induced model study, treatment with Rg1 eliminated H_2O_2-induced different morphological fluctuations such as cell rounding, membrane blebbing, neurite retraction, and nuclei condensation. The mechanism of neuroprotection of Rg1 is connected to the inhibition of myosin IIA−actin interaction and the signaling pathway of Rho-associated kinase 1/Myosin light-chain kinase [92].

4. Conclusion

Recently, medicinal plants have shown potent pharmacological roles in various disorders that have been proven in several preclinical and clinical studies. Identifying the proper therapeutic targets is essential to setting up treatment strategies for various neurological disorders. In case of NDDs, no cure has yet been discovered, and this is a major topic of research today. In addition, identifying therapeutic targets and therapeutic molecules are crucial steps for the designing of therapeutic management for NDDs. Considering the importance of having targets, several signals have demonstrated a potential pharmacological role in various neurological disorders. Detecting these targets, allows the possibility to discover novel compounds suitable to treat the NDDs. Ginseng and its active substances have been known as multipotential therapeutics against various acute and chronic diseases. With respect to their multipotential role, researchers have concentrated their research. Various reports have indicated that they may be great therapeutic agents for neurological disorders due to their potential activities that modulate the various molecular signaling pathways.

However, research has not concluded how ginseng active compounds can have specific medicinal effects on NDDs. We focused on NDDs and here present the ion channels and specific molecular signals that are modulated by ginseng and its active substances. The overview shows that ginseng components might emerge as candidates for NDDs due to their versatile potential, specifically, their neuroprotective activities against neuroinflammation and apoptotic cell death. It might be helpful to conduct deeper research and clinical trials regarding NDDs. Also, based on signal modulating potential, molecular modification of ginseng compounds may be useful in obtaining superior pharmaceutical drugs. In addition, understanding of the complex response to ginseng could allow developing synergistic drug therapy.

To examine and validate the potential, several disease models were designed including toxin-induced cellular and animal models as well as transgenic models to conduct for different NDDs. Further studies concerning specific ion channels and molecular signals known in the pathogenesis and as therapeutic targets for NDDs are suggested to confirm the exact pharmacological and therapeutic activities of ginseng and its active compounds. The design and execution of clinical studies for active ginseng compounds to treat NDDs is a major challenge for the clinical scientist. Before clinical studies, more investigations using laboratory-based and informatics-based approaches should be conducted to understand the precise medicinal efficacy, potency, and safety in the NDDs. These approaches might give direction to modify and synthesize new derivatives of active ginseng compounds targeting the NDDs. Finally, the diverse potential role of ginseng active compounds might serve a good role in treatment strategies to cure NDDs. In near future, rigorous studies of active ginseng compounds with their modified forms will produce drugs for therapy of NDDs.

Conflicts of interest

The authors have no conflicts of interest.

Acknowledgment

This research was supported by The Leading Human Resource Training Program of Regional Neo industry through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT and Future Planning (grant number: NRF-2016 H1D5A1909610).

References

[1] Sheikh S, Haque E, Mir SS. Neurodegenerative diseases: multifactorial conformational diseases and their therapeutic interventions. J Neurodegener Dis 2013;2013:8.
[2] Błaszczyk JW. Parkinson's disease and neurodegeneration: GABA-collapse hypothesis. Front Neurosci 2016;10.
[3] Carrell RW, Lomas DA. Conformational disease. Lancet 1997;350(9071):134−8.
[4] Kovacs GG. Molecular pathological classification of neurodegenerative diseases: turning towards precision medicine. Int J Mol Sci 2016;17(2):189.
[5] Chen X, Pan W. The treatment strategies for neurodegenerative diseases by integrative medicine. Integr Med Int 2014;1(4):223−5.
[6] Xiang YZ, Shang HC, Gao XM, Zhang BL. A comparison of the ancient use of ginseng in traditional Chinese medicine with modern pharmacological experiments and clinical trials. Phytother Res 2008;22(7):851−8.
[7] Hwang IH, Kwon YK, Cho CK, Lee YW, Sung JS, Joo JC, Lee KB, Yoo HS, Jang IS. Modified *Panax ginseng* extract inhibits uPAR-mediated α 5 β1-integrin signaling by modulating caveolin-1 to induce early apoptosis in lung cancer cells. Am J Chin Med 2016;44(05):1081−97.
[8] Leung KW, Wong AS. Ginseng and male reproductive function. Spermatogenesis 2013;3(3):e26391.
[9] Nocerino E, Amato M, Izzo AA. The aphrodisiac and adaptogenic properties of ginseng. Fitoterapia 2000;71:S1−5.
[10] Lee JS, Hwang HS, Ko EJ, Lee YN, Kwon YM, Kim MC, Kang SM. Immunomodulatory activity of red ginseng against influenza A virus infection. Nutrients 2014;6(2):517−29.
[11] Hong M, Lee YH, Kim S, Suk KT, Bang CS, Yoon JH, Baik GH, Kim DJ, Kim MJ. Anti-inflammatory and antifatigue effect of Korean Red Ginseng in patients with nonalcoholic fatty liver disease. J Ginseng Res 2016;40(3):203−10.
[12] Yu T, Rhee MH, Lee J, Kim SH, Yang Y, Kim HG, Kim Y, Kim C, Kwak Y-S, Kim J-H. Ginsenoside Rc from Korean Red Ginseng (*Panax ginseng* CA Meyer) attenuates inflammatory symptoms of gastritis, hepatitis and arthritis. Am J Chin Med 2016;44(03):595−615.
[13] Kim MH, Lee EJ, Cheon JM, Nam KJ, Oh TH, Kim KS. Antioxidant and hepatoprotective effects of fermented red ginseng against high fat diet-induced hyperlipidemia in rats. Lab Anim Res 2016;32(4):217−23.
[14] Kim HJ, Lee SG, Chae IG, Kim MJ, Im NK, Yu MH, Lee EJ, Lee IS. Antioxidant effects of fermented red ginseng extracts in streptozotocin-induced diabetic rats. J Ginseng Res 2011;35(2):129−37.
[15] Hwang E, Park SY, Yin CS, Kim HT, Kim YM, Yi TH. Antiaging effects of the mixture of *Panax ginseng* and *Crataegus pinnatifida* in human dermal fibroblasts and healthy human skin. J Ginseng Res 2017;41(1):69−77.
[16] Chen XJ, Zhang XJ, Shui YM, Wan JB, Gao JL. Anticancer activities of protopanaxadiol-and protopanaxatriol-type ginsenosides and their metabolites. Evid Based Complement Alternat Med 2016;2016.
[17] Im K, Kim J, Min H. Ginseng, the natural effectual antiviral: protective effects of Korean Red Ginseng against viral infection. J Ginseng Res 2016;40(4):309−14.
[18] Uzkeser M, Karakus E, Albayrak A, Kiki İ, Bayir Y, Cadirci E, Unal D, Halici Z, Karadeniz A. Protective effect of *Panax ginseng* against N-acetyl-p-aminophenol-induced hepatotoxicity in rats. African J Pharmacy and Pharmacol 2012;6(36):2634−42.
[19] Lim KH, Ko D, Kim JH. Cardioprotective potential of Korean Red Ginseng extract on isoproterenol-induced cardiac injury in rats. J Ginseng Res 2013;37(3):273−82.
[20] Lee LS, Cho CW, Hong HD, Lee YC, Choi UK, Kim YC. Hypolipidemic and antioxidant properties of phenolic compound-rich extracts from white ginseng (*Panax ginseng*) in cholesterol-fed rabbits. Molecules 2013;18(10):12548−60.

[21] Shin HS, Yu M, Kim M, Choi HS, Kang DH. Renoprotective effect of red ginseng in gentamicin-induced acute kidney injury. Lab Investig 2014;94(10):1147–60.

[22] Kim EH, Kim IH, Ha JA, Choi KT, Pyo S, Rhee DK. Antistress effect of red ginseng in brain cells is mediated by TACE repression via PADI4. J Ginseng Res 2013;37(3):315–23.

[23] Kim Y, Choi EH, Doo M, Kim JY, Kim CJ, Kim CT, Kim IH. Anti-stress effects of ginseng via down-regulation of tyrosine hydroxylase (TH) and dopamine β-hydroxylase (DBH) gene expression in immobilization-stressed rats and PC12 cells. Nutr Res Prac 2010;4(4):270–5.

[24] Feng L, Liu XM, Cao FR, Wang LS, Chen YX, Liao YH, Wang Q, Chang Q. Anti-stress effects of ginseng total saponins on hindlimb-unloaded rats assessed by a metabolomics study. J Ethnopharmacol 2016;188:39–47.

[25] Dang H, Chen Y, Liu X, Wang Q, Wang L, Jia W, Wang Y. Antidepressant effects of ginseng total saponins in the forced swimming test and chronic mild stress models of depression. Prog Neuropsychopharmacol Biol Psychiatry 2009;33(8):1417–24.

[26] He DF, Ren YP, Liu MY. Effects of ginseng fruit saponins on serotonin system in Sprague-Dawley rats with myocardial infarction, depression, and myocardial infarction complicated with depression. Chin Med J (Engl) 2016;129(24):2913.

[27] Liao B, Newmark H, Zhou R. Neuroprotective effects of ginseng total saponin and ginsenosides Rb1 and Rg1 on spinal cord neurons in vitro. Exp Neurol 2002;173(2):224–34.

[28] Van Kampen J, Robertson H, Hagg T, Drobitch R. Neuroprotective actions of the ginseng extract G115 in two rodent models of Parkinson's disease. Exp Neurol 2003;184(1):521–9.

[29] Naval M, Gómez-Serranillos M, Carretero M, Villar A. Neuroprotective effect of a ginseng (*Panax ginseng*) root extract on astrocytes primary culture. J Ethnopharmacol 2007;112(2):262–70.

[30] Seo JY, Ju SH, Oh J, Lee SK, Kim JS. Neuroprotective and cognition-enhancing effects of compound K isolated from red ginseng. J Agric Food Chem 2016;64(14):2855–64.

[31] Christensen LP. Ginsenosides: chemistry, biosynthesis, analysis, and potential health effects. Adv Food Nutr Res 2008;55:1–99.

[32] Radad K, Moldzio R, Rausch WD. Ginsenosides and their CNS targets. CNS Neu Ther 2011;17(6):761–8.

[33] Rokot NT, Kairupan TS, Cheng KC, Runtuwene J, Kapantow NH, Amitani M, Morinaga A, Amitani H, Asakawa A, Inui A. A role of ginseng and its constituents in the treatment of central nervous system disorders. Evid Based Complement Alternat Med 2016;2016.

[34] Yeo HB, Yoon HK, Lee HJ, Kang SG, Jung KY, Kim L. Effects of Korean red ginseng on cognitive and motor function: a double-blind, randomized, placebo-controlled trial. J Ginseng Res 2012;36(2):190–7.

[35] Kim JH, Hong YH, Lee JH, Kim DH, Nam G, Jeong SM, Lee BH, Lee SM, Nah SY. A role for the carbohydrate portion of ginsenoside Rg 3 in Na^+ channel inhibition. Mol Cells 2005;19(1):137–42.

[36] Lee JH, Jeong SM, Kim JH, Lee BH, Yoon IS, Lee JH, Choi SH, Kim DH, Rhim H, Kim SS. Characteristics of ginsenoside Rg3-mediated brain Na^+ current inhibition. Mol Pharmacol 2005;68(4):1114–26.

[37] Duan Y, Nicholson RA. 20 (S)-protopanaxadiol and the ginsenoside Rh 2 inhibit Na^+ channel-activated depolarization and Na^+ channel-dependent amino acid neurotransmitter release in synaptic fractions isolated from mammalian brain. Comp Biochem Physiol C Toxicol Pharmacol 2008;147(3):351–6.

[38] Choi SH, Shin TJ, Lee BH, Hwang SH, Lee SM, Lee BC, Park CS, Ha TS, Nah SY. Ginsenoside Rg3 enhances large conductance Ca^{2+}-activated potassium channel currents: a role of Tyr360 residue. Mol Cells 2011 Feb;31(2):133–40.

[39] Choi S, Jung SY, Ko YS, Koh SR, Rhim H, Nah SY. Functional expression of a novel ginsenoside Rf binding protein from rat brain mRNA in Xenopus laevis oocytes. Mol Pharm 2002;61(4):928–35.

[40] Kim S, Nah SY, Rhim H. Neuroprotective effects of ginseng saponins against L-type Ca^{2+} channel-mediated cell death in rat cortical neurons. Biochem Biophys Res Commun 2008;365(3):399–405.

[41] Choi SH, Lee BH, Hwang SH, Kim HJ, Lee SM, Kim HC, Rhim HW, Nah SY. Molecular mechanisms of large-conductance Ca^{2+}-activated potassium channel activation by ginseng gintonin. Evid Based Complement Alternat Med 2013;2013.

[42] Zhang YF, Fan XJ, Li X, Peng LL, Wang GH, Ke KF, Jiang ZL. Ginsenoside Rg 1 protects neurons from hypoxic–ischemic injury possibly by inhibiting Ca^{2+} influx through NMDA receptors and L-type voltage-dependent Ca^{2+} channels. Eur J Pharmacol 2008;586(1):90–9.

[43] Quan QK, Li X, Yuan HF, Wang Y, Liu WL. Ginsenoside Rg1 inhibits high-voltage-activated calcium channel currents in hippocampal neurons of beta-amyloid peptide-exposed rat brain slices. Chinese J Integr Med 2016:1–6.

[44] Lin ZY, Chen LM, Zhang J, Pan XD, Zhu YG, Ye QY, Huang HP, Chen XC. Ginsenoside Rb1 selectively inhibits the activity of L-type voltage-gated calcium channels in cultured rat hippocampal neurons. Acta Pharmacol Sin 2012;33(4):438–44.

[45] Choi S, Jung SY, Lee JH, Sala F, Criado M, Mulet J, Valor LM, Sala S, Engel AG, Nah SY. Effects of ginsenosides, active components of ginseng, on nicotinic acetylcholine receptors expressed in Xenopus oocytes. Eur J Pharmacol 2002;442(1):37–45.

[46] Sala F, Mulet J, Choi S, Jung SY, Nah SY, Rhim H, Valor LM, Criado M, Sala S. Effects of ginsenoside Rg2 on human neuronal nicotinic acetylcholine receptors. J Pharmacol Exp Ther 2002;301(3):1052–9.

[47] Lee BH, Choi SH, Hwang SH, Kim HJ, Lee SM, Kim HC, Rhim H, Nah SY. Effects of ginsenoside Rg3 on α9α10 nicotinic acetylcholine receptor-mediated ion currents. Biol Pharm Bull 2013;36(5):812–8.

[48] Jin Y, Peng J, Wang X, Zhang D, Wang T. Ameliorative effect of ginsenoside Rg1 on lipopolysaccharide-induced cognitive impairment: role of cholinergic system. Neurochem Res 2017;42(5):1299–307.

[49] Kim MS, Yu JM, Kim HJ, Kim HB, Kim ST, Jang SK, Choi YW, Lee DI, Joo SS. Ginsenoside Re and Rd enhance the expression of cholinergic markers and neuronal differentiation in Neuro-2a cells. Biol Pharm Bull 2014;37(5):826–33.

[50] Kimura T, Saunders P, Kim H, Rheu H, Oh K, Ho I. Interactions of ginsenosides with ligand-bindings of GABAA and GABAB receptors. Gen Pharmacol 1994;25(1):193–9.

[51] Kim HS, Hwang SL, Nah SY, Oh S. Changes of [3H] MK-801,[3H] muscimol and [3H] flunitrazepam binding in rat brain by the prolonged ventricular infusion of ginsenoside Rc and Rg1. Pharmacol Res 2001;43(5):473–9.

[52] Choi SE, Choi S, Lee JH, Whiting PJ, Lee SM, Nah SY. Effects of ginsenosides on GABA A receptor channels expressed in Xenopus oocytes. Arch Pharm Res 2003;26(1):28–33.

[53] Lee BH, Choi SH, Shin TJ, Hwang SH, Kang J, Kim HJ, Kim BJ, Nah SY. Effects of ginsenoside metabolites on GABAA receptor-mediated ion currents. J Ginseng Res 2012;36(1):55.

[54] Bae MY, Cho JH, Choi IS, Park HM, Lee MG, Kim DH, Jang IS. Compound K, a metabolite of ginsenosides, facilitates spontaneous GABA release onto CA3 pyramidal neurons. J Neurochem 2010;114(4):1085–96.

[55] Chanana P, Kumar A. GABA-BZD receptor modulating mechanism of panax quinquefolius against 72-h sleep deprivation induced anxiety like behavior: possible roles of oxidative stress, mitochondrial dysfunction and neuroinflammation. Front Neurosci 2016;10.

[56] Kim S, Ahn K, Oh TH, Nah SY, Rhim H. Inhibitory effect of ginsenosides on NMDA receptor-mediated signals in rat hippocampal neurons. Biochem Biophys Res Commun 2002;296(2):247–54.

[57] Seong Y, ChangSik S, HackSeang K. Inhibitory effect of ginseng total saponins on glutamate-induced swelling of cultured astrocytes. Biol Pharm Bull 1995;18(12):1776–8.

[58] Kim Y, Kim S, Markelonis G, Oh T. Ginsenosides Rb1 and Rg3 protect cultured rat cortical cells from glutamate-induced neurodegeneration. J Neurosci Res 1998;53(4):426–32.

[59] Wu J, Jeong HK, Bulin SE, Kwon SW, Park JH, Bezprozvanny I. Ginsenosides protect striatal neurons in a cellular model of Huntington's disease. J Neurosci Res 2009;87(8):1904–12.

[60] Gu B, Nakamichi N, Zhang WS, Nakamura Y, Kambe Y, Fukumori R, Takuma K, Yamada K, Takarada T, Taniura H. Possible protection by notoginsenoside R1 against glutamate neurotoxicity mediated by N-methyl-D-aspartate receptors composed of an NR1/NR2B subunit assembly. J Neurosci Res 2009;87(9):2145–56.

[61] Yoon SR, Nah JJ, Shin YH, Kim SK, Nam KY, Choi HS, Nah SY. Ginsenosides induce differential antinociception and inhibit substance P induced-nociceptive response in mice. Life Sci 1998;62(21):319–25.

[62] Shin YH, Jung OM, Nah JJ, Nam KY, Kim CY, Nah SY. Ginsenosides that produce differential antinociception in mice. Gen Pharmacol 1999;32(6):653–9.

[63] Lee JH, Kim SR, Bae CS, Kim D, Hong HN, Nah SY. Protective effect of ginsenosides, active ingredients of *Panax ginseng*, on kainic acid-induced neurotoxicity in rat hippocampus. Neurosci Lett 2002;325(2):129–33.

[64] Peng LL, Shen HM, Jiang ZL, Li X, Wang GH, Zhang YF, Ke KF. Inhibition of NMDA receptors underlies the neuroprotective effect of ginsenoside Rb3. Am J Chin Med 2009;37(4):759–70.

[65] Lee E, Kim S, Chung KC, Choo MK, Kim DH, Nam G, Rhim H. 20 (S)-ginsenoside Rh 2, a newly identified active ingredient of ginseng, inhibits NMDA receptors in cultured rat hippocampal neurons. Eur J Pharmacol 2006;536(1):69–77.

[66] Kim JH, Cho SY, Lee JH, Jeong SM, Yoon IS, Lee BH, Lee JH, Pyo MK, Lee S-M, Chung JM. Neuroprotective effects of ginsenoside Rg 3 against homocysteine-induced excitotoxicity in rat hippocampus. Brain Res 2007;1136:190–9.

[67] Shin TJ, Hwang SH, Choi SH, Lee BH, Kang J, Kim HJ, Zukin RS, Rhim H, Nah SY. Effects of protopanaxatriol-ginsenoside metabolites on rat N-methyl-d-aspartic Acid receptor-mediated ion currents. Korean J Physiol Pharmacol 2012;16(2):113–8.

[68] Chen WZ, Liu S, Chen FF, Zhou CJ, Yu J, Zhuang CL, Shen X, Chen BC, Yu Z. Prevention of postoperative fatigue syndrome in rat model by ginsenoside Rb1 via down-regulation of inflammation along the NMDA receptor pathway in the hippocampus. Biol Pharm Bull 2015;38(2):239–47.

[69] Zhao BS, Liu Y, Gao XY, Zhai HQ, Guo JY, Wang XY. Effects of ginsenoside Rg1 on the expression of toll-like receptor 3, 4 and their signalling transduction factors in the NG108-15 murine neuroglial cell line. Molecules 2014;19(10):16925–36.

[70] Bak MJ, Hong SG, Lee JW, Jeong WS. Red ginseng marc oil inhibits iNOS and COX-2 via NFκB and p38 pathways in LPS-stimulated RAW 264.7 macrophages. Molecules 2012;17(12):13769–86.

[71] Fan Y, Sun C, Gao X, Wang F, Li X, Kassim RM, Tai G, Zhou Y. Neuroprotective effects of ginseng pectin through the activation of ERK/MAPK and Akt survival signaling pathways. Mol Med Rep 2012;5(5):1185–90.

[72] Ahn S, Singh P, Castro-Aceituno V, Yesmin Simu S, Kim YJ, Mathiyalagan R, Yang DC. Gold nanoparticles synthesized using *Panax ginseng* leaves suppress inflammatory-mediators production via blockade of NF-κB activation in macrophages. Artif Cells Nanomed Biotechnol 2017;45(2):270–6.

[73] Saba E, Jeon BR, Jeong DH, Lee K, Goo YK, Kwak D, Kim S, Roh SS, Kim SD, Nah SY. A novel Korean Red Ginseng compound gintonin inhibited inflammation by MAPK and NF-κB pathways and recovered the levels of mir-34a and mir-93 in RAW 264.7 cells. Evid Based Complement Alternat Med 2015;2015.

[74] Song J, Chen X, Zhang J, Huang T, Zeng Y, Shen J, Chen L. JNK/p38 MAPK involves in ginsenoside Rb1 attenuating beta-amyloid peptide (25-35)-induced tau protein hyperphosphorylation in embryo rat cortical neurons. Yao Xue Xue Bao 2008;43(1):29–34.

[75] Hashimoto R, Yu J, Koizumi H, Ouchi Y, Okabe T. Ginsenoside Rb1 prevents MPP^+-induced apoptosis in PC12 cells by stimulating estrogen receptors with consequent activation of ERK1/2, Akt and inhibition of SAPK/JNK, p38 MAPK. Evid Based Complement Alternat Med 2012;2012.

[76] Wu SD, Xia F, Lin XM, Duan KL, Wang F, Lu QL, Cao H, Qian YH, Shi M. Ginsenoside-Rd promotes neurite outgrowth of PC12 cells through MAPK/ERK-and PI3K/AKT-dependent pathways. Int J Mol Sci 2016;17(2):177.

[77] Cong L, Chen W. Neuroprotective effect of ginsenoside Rd in spinal cord injury rats. Basic Clin Pharmacol Toxicol 2016;119(2):193–201.

[78] Lu MC, Lai TY, Hwang JM, Chen HT, Chang SH, Tsai FJ, Wang HL, Lin CC, Kuo WW, Huang CY. Proliferation-and migration-enhancing effects of ginseng and ginsenoside Rg1 through IGF-I-and FGF-2-signaling pathways on RSC96 Schwann cells. Cell Biochem Funct 2009;27(4):186–92.

[79] Zong Y, Ai QL, Zhong LM, Dai JN, Yang P, He Y, Sun J, Ling EA, Lu D. Ginsenoside Rg1 attenuates lipopolysaccharide-induced inflammatory responses via the phospholipase C-γ1 signaling pathway in murine BV-2 microglial cells. Curr Med Chem 2012;19(5):770–9.

[80] Huang L, Liu LF, Liu J, Dou L, Wang GY, Liu XQ, Yuan QL. Ginsenoside Rg1 protects against neurodegeneration by inducing neurite outgrowth in cultured hippocampal neurons. Neural Regen Res 2016;11(2):319–25.

[81] Hu JF, Xue W, Ning N, Zhang JT, Chen NH. Ginsenoside Rg1 activated CaMKIIα mediated extracellular signal-regulated kinase/mitogen activated protein kinase signaling pathway. Acta Pharmacol Sin 2008;29(9):1119–26.

[82] Lee YY, Park JS, Jung JS, Kim DH, Kim HS. Anti-inflammatory effect of ginsenoside Rg5 in lipopolysaccharide-stimulated BV2 microglial cells. Int J Mol Sci 2013;14(5):9820–33.

[83] Meng X, Sun G, Ye J, Xu H, Wang H, Sun X. Notoginsenoside R1-mediated neuroprotection involves estrogen receptor-dependent crosstalk between Akt and ERK1/2 pathways: a novel mechanism of Nrf2/ARE signaling activation. Free Radic Res 2014;48(4):445–60.

[84] Jung SH, Woo MS, Kim SY, Kim WK, Hyun JW, Kim EJ, Kim DH, Kim HS. Ginseng saponin metabolite suppresses phorbol ester–induced matrix metalloproteinase-9 expression through inhibition of activator protein-1 and mitogen-activated protein kinase signaling pathways in human astroglioma cells. Int J Cancer 2006;118(2):490–7.

[85] Zhang Y, Lin L, Liu G, Liu J, Li T. Pharmacokinetics and brain distribution of ginsenosides after administration of sailuotong. Zhongguo Zhong Yao Za Zhi 2014;39(2):316–21.

[86] Tan X, Gu J, Zhao B, Wang S, Yuan J, Wang C, Chen J, Liu J, Feng L, Jia X. Ginseng improves cognitive deficit via the RAGE/NF-κB pathway in advanced glycation end product-induced rats. J Ginseng Res 2015;39(2):116–24.

[87] Liu J, Yan X, Li L, Li Y, Zhou L, Zhang X, Hu X, Zhao G. Ginsenoside Rd improves learning and memory ability in APP transgenic mice. J Mol Neurosci 2015;57(4):522–8.

[88] Kim J, Shim J, Lee S, Cho WH, Hong E, Lee JH, Han JS, Lee HJ, Lee KW. Rg3-enriched ginseng extract ameliorates scopolamine-induced learning deficits in mice. BMC Complement Altern Med 2016;16(1):66.

[89] Lee KW, Jung SY, Choi SM, Yang EJ. Effects of ginsenoside Re on LPS-induced inflammatory mediators in BV2 microglial cells. BMC Complement Altern Med 2012;12(1):196.

[90] Jung JS, Shin JA, Park EM, Lee JE, Kang YS, Min SW, Kim DH, Hyun JW, Shin CY, Kim HS. Anti-inflammatory mechanism of ginsenoside Rh1 in lipopolysaccharide-stimulated microglia: critical role of the protein kinase A pathway and hemeoxygenase-1 expression. J Neurochem 2010;115(6):1668–80.

[91] Kou J, Liu Q, Guan T, Wang Y, Lv Y, Huang Y, Cao Z, Yu B. Ginsenoside Rg1 protects hydrogen peroxide-induced PC12 cell death: involvement of NMMHC IIA-NF-κB/p65 pathway (1143.15). The FASEB J 2014;28(1). 1143–1215.

[92] Wang Y, Liu Q, Xu Y, Zhang Y, Lv Y, Tan Y, Jiang N, Cao G, Ma X, Wang J. Ginsenoside Rg1 protects against oxidative stress-induced neuronal apoptosis through myosin IIA-actin related cytoskeletal reorganization. Int J Biol Sci 2016;12(11):1341.

[93] Zhao P, Teng J, Zhu H, Zheng Y, Zhu X. Ginsenoside Rg1 prevents MPP^+-induced apoptosis of SHSY5Y cells via the inhibition of a Bax-mediated mitochondrial pathway and by suppressing oxidative stress. Int J Clin Exp Med 2016;9(6):10811–9.

[94] Hou J, Xue J, Lee M, Sung C. Ginsenoside Rd as a potential neuroprotective agent prevents trimethyltin injury. Biomed Rep 1899;6(4):435–40.

[95] Liu D, Zhang H, Gu W, Liu Y, Zhang M. Neuroprotective effects of ginsenoside Rb1 on high glucose-induced neurotoxicity in primary cultured rat hippocampal neurons. PLoS One 2013;8(11):e79399.

[96] Li H, Kang T, Qi B, Kong L, Jiao Y, Cao Y, Zhang J, Yang J. Neuroprotective effects of ginseng protein on PI3K/Akt signaling pathway in the hippocampus of d-galactose/AlCl 3 inducing rats model of Alzheimer's disease. J Ethnopharmacol 2016;179:162–9.

[97] Zhang X, Shi M, Bjørås M, Wang W, Zhang G, Han J, Liu Z, Zhang Y, Wang B, Chen J. Ginsenoside Rd promotes glutamate clearance by up-regulating glial glutamate transporter GLT-1 via PI3K/AKT and ERK1/2 pathways. Front Pharmacol 2013;4:152.

[98] Liu Y, Zhang R-Y, Zhao J, Dong Z, Feng D-Y, Wu R, Shi M, Zhao G. Ginsenoside Rd protects SH-SY5Y cells against 1-methyl-4-phenylpyridinium induced injury. Int J Mol Sci 2015;16(7):14395–408.

[99] Wang X, Wang C, Wang J, Zhao S, Zhang K, Wang J, Zhang W, Wu C, Yang J. Pseudoginsenoside-F11 (PF11) exerts anti-neuroinflammatory effects on LPS-activated microglial cells by inhibiting TLR4-mediated TAK1/IKK/NF-κB, MAPKs and Akt signaling pathways. Neuropharmacology 2014;79:642–56.

[100] Gao QG, Chen WF, Xie JX, Wong MS. Ginsenoside Rg1 protects against 6-OHDA-induced neurotoxicity in neuroblastoma SK-N-SH cells via IGF-I receptor and estrogen receptor pathways. J Neurochem 2009;109(5):1338–47.

[101] Xu L, Chen WF, Wong MS. Ginsenoside Rg1 protects dopaminergic neurons in a rat model of Parkinson's disease through the IGF-I receptor signalling pathway. Br J Pharmacol 2009;158(3):738–48.

[102] Choi JH, Lee MJ, Jang M, Kim HJ, Lee S, Lee SW, Kim YO, Cho IH. *Panax ginseng* exerts antidepressant-like effects by suppressing neuroinflammatory response and up-regulating Nrf2 signaling in the amygdala. J Ginseng Res 2018;42(1):107–15.

[103] Ye J, Yao JP, Wang X, Zheng M, Li P, He C, Wan JB, Yao X, Su H. Neuroprotective effects of ginsenosides on neural progenitor cells against oxidative injury. Mol Med Rep 2016;13(4):3083–91.

[104] Ni N, Liu Q, Ren H, Wu D, Luo C, Li P, Wan JB, Su H. Ginsenoside Rb1 protects rat neural progenitor cells against oxidative injury. Molecules 2014;19(3):3012–24.

[105] Du X, Xu H, Jiang H, Xie J. Akt/Nrf2 activated upregulation of heme oxygenase-1 involves in the role of Rg1 against ferrous iron-induced neurotoxicity in SK-N-SH cells. Neurotox Res 2013;24(1):71–9.

[106] Lee YY, Park JS, Lee EJ, Lee SY, Kim DH, Kang JL, Kim HS. Anti-inflammatory mechanism of ginseng saponin metabolite Rh3 in lipopolysaccharide-stimulated microglia: critical role of 5′-adenosine monophosphate-activated protein kinase signaling pathway. J Agric Food Chem 2015;63(13):3472–80.

[107] Gao Y, Chu SF, Li JP, Zhang Z, Yan JQ, Wen ZL, Xia CY, Mou Z, Wang ZZ, He WB, et al. Protopanaxtriol protects against 3-nitropropionic acid-induced oxidative stress in a rat model of Huntington's disease. Acta Pharmacol Sin 2015;36(3):311–22.

[108] Hussein J, Refaat E, Medhat D, El-Bana M, Latif YA, Farrag AR, Nazeef N, Moify M. *Panax ginseng* attenuates experimental brain injury by increasing brainderived neurotrophic factor and inhibition of neuroinflammation. J Chem Pharm Res 2016;8(1):186–95.

[109] Si Y, Zhu J, Huang X, Zhu P, Xie C. Effects of *Panax notoginseng* saponins on proliferation and differentiation of rat embryonic cortical neural stem cells. J Chin Med Assoc 2016;79(5):256–63.

[110] Li F, Wu X, Li J, Niu Q. Ginsenoside Rg1 ameliorates hippocampal long-term potentiation and memory in an Alzheimer's disease model. Mol Med Rep 2016;13(6):4904–10.

[111] Zhu G, Wang Y, Li J, Wang J. Chronic treatment with ginsenoside Rg1 promotes memory and hippocampal long-term potentiation in middle-aged mice. Neuroscience 2015;292:81–9.

[112] Gao XQ, Yang CX, Chen GJ, Wang GY, Chen B, Tan SK, Liu J, Yuan QL. Ginsenoside Rb1 regulates the expressions of brain-derived neurotrophic factor and caspase-3 and induces neurogenesis in rats with experimental cerebral ischemia. J Ethnopharmacol 2010;132(2):393–9.

[113] Jiang Z, Wang Y, Zhang X, Peng T, Lu Y, Leng J, Xie Q. Preventive and therapeutic effects of ginsenoside Rb1 for neural injury during cerebral infarction in rats. Am J Chin Med 2013;41(02):341–52.

[114] Cui J, Jiang L, Xiang H. Ginsenoside Rb3 exerts antidepressant-like effects in several animal models. J Psychopharmacol 2012;26(5):697–713.

[115] Jiang B, Xiong Z, Yang J, Wang W, Wang Y, Hu ZL, Wang F, Chen JG. Antidepressant-like effects of ginsenoside Rg1 are due to activation of the BDNF signalling pathway and neurogenesis in the hippocampus. Br J Pharmacol 2012;166(6):1872–87.

[116] Zhu X, Gao R, Liu Z, Cheng Z, Qi Y, Fan C, Yu SY. Ginsenoside Rg1 reverses stress-induced depression-like behaviours and brain-derived neurotrophic factor expression within the prefrontal cortex. Eur J Neurosci 2016;44(2):1878–85.

[117] You Z, Yao Q, Shen J, Gu Z, Xu H, Wu Z, Chen C, Li L. Antidepressant-like effects of ginsenoside Rg3 in mice via activation of the hippocampal BDNF signaling cascade. J Nat Med 2016:1–13.

[118] Guo J, Chang L, Zhang X, Pei S, Yu M, Gao J. Ginsenoside compound K promotes β-amyloid peptide clearance in primary astrocytes via autophagy enhancement. Exp Ther Med 2014;8(4):1271–4.

[119] Zhou T, Zu G, Zhang X, Wang X, Li S, Gong X, Liang Z, Zhao J. Neuroprotective effects of ginsenoside Rg1 through the Wnt/β-catenin signaling pathway in both *in vivo* and *in vitro* models of Parkinson's disease. Neuropharmacology 2016;101:480–9.