Neuroprotective Mechanisms of Ginsenoside Rb1 in Central Nervous System Diseases

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Panax ginseng and Panax notoginseng, two well-known herbs with enormous medical value in Asian countries, have a long usage history in China for the therapy of some diseases, such as stroke. Ginsenoside Rb1 is one of most important active ingredients in Panax ginseng and Panax notoginseng. In the last two decades, more attention has focused on ginsenoside Rb1 as an antioxidative, anti-apoptotic and anti-inflammatory agent that can protect the nervous system. In the review, we summarize the neuroprotective roles of ginsenoside Rb1 and its potential mechanisms in central nervous system diseases (CNSDs), including neurodegenerative diseases, cerebral ischemia injury, depression and spinal cord injury. In conclusion, ginsenoside Rb1 has a potential neuroprotection due to its inhibition of oxidative stress, apoptosis, neuroinflammation and autophagy in CNSDs and may be a promising candidate agent for clinical therapy of CNSDs in the future.

Keywords: central nervous system diseases, ginsenoside Rb1, neuroprotection, mechanisms, antioxidant

INTRODUCTION

Panax ginseng and Panax notoginseng are two valuable medicinal herbs in the genus Panax, family Araliaceae (Wang et al., 2016). The curative effects of Panax ginseng and Panax notoginseng were first detailedly recorded by Shizhen Li in “Compendium of Materia Medica,” which was praised by Darwin as “the Encyclopedia of ancient China.” Panax ginseng and Panax notoginseng have a wide and significant application in medicinal purposes and economic values (Qiao et al., 2018). In China Panax ginseng has a more than 5,000 years of application history (Yun, 2001) and was recorded in the world’s oldest pharmacopoeia of medicinal herbs and plants, “Shennong’s Herbal Classic” (Shi et al., 2019). Panax ginseng mainly grows in the mountains of East Asia countries, particularly in China, Korea and Japan (Baeg and So, 2013). Shizhen Li described Panax ginseng as a magic medicine that can almost cure all diseases. Since the content of active ingredient in Panax notoginseng is higher than that in Panax ginseng, Panax notoginseng enjoys a reputation for “The King in Panax.” In modern times, they have received considerable interest due to their extensive application in healthcare products, clinical therapy, and as foods and food additives in the whole world (Yang et al., 2014) because they could relieve stress and fatigue, prevent aging, increase vigor and strength the body and mind (Choi, 2008; Kim et al., 2015). Panax ginseng and Panax notoginseng are often used to slow down the symptoms, such as traumatic injury, blood stasis, swelling and pain (Tianhong et al., 2014; Chen et al., 2017; Wu et al., 2018). The ginsenosides, chemical constituents found in Panax ginseng and Panax notoginseng, can inhibit the effects of inflammatory cytokines, block signaling pathways that induce inflammation, and inhibit cells that participate in inflammatory processes (de Oliveira Zanuso et al., 2022). What’s more, increasing
evidence has demonstrated that ginsenosides are involved in neuroprotective effects in the central nervous system diseases due to their antioxidant, anti-apoptotic, and anti-inflammatory features (Lu et al., 2022).

GINSENOside RB1

Many studies support that the beneficial effects of Panax ginseng attributed to ginsenosides (Qi et al., 2011). Triterpenoid plays an important role in the medical value of Panax ginseng and Panax notoginseng (Ng, 2006). Triterpenoid is constituted mainly by ginsenoside Rb1, ginsenoside Rb2, and notoginsenoside R1, among which ginsenoside Rb1 takes up a tremendous part. Ginsenoside is a kind of steroids, also known as triterpenoid saponins. All the ginsenosides have the similarity in the basic structure, containing sterane steroid nuclei arranged into four rings by 30 carbon atoms (Cheng et al., 2019). Results also indicate that the function of ginsenoside Rb1 is superior to the function of ginsenoside Rb2, because ginsenoside Rb1 is a panaxtriol with two sugars and ginsenoside Rb2 is a panaxtriol with four sugars (Kim et al., 2014). The structure of ginsenoside Rb1 is shown in Figure 1.

PHARMACOLOGICAL EFFECTS OF GINSENOside RB1

With the development of the study, ginsenoside Rb1 presents antioxidant, anti-apoptotic, and anti-inflammatory properties. In a cell free system, ginsenoside Rb1 can significantly and selectively scavenge hydroxyl radical and hypochlorous acid, two of the strongest reactive oxygen species (ROS), and protect biomacromolecules from oxidative damage (Lu et al., 2012). Ginsenoside Rb1 could inhibit mitochnondria-, endoplasmic reticulum stress- and death receptor-mediated apoptotic pathways (Ke et al., 2021; Shaukat et al., 2021). Our previous study demonstrated that ginsenoside Rb1 inhibited oxidative stress-induced endoplasmic reticulum stress in rat PC12 cells (Zeng et al., 2015). What’s more, treatment with ginsenoside Rb1 attenuated tumor necrosis factor-α (TNF-α)-induced inflammation by inhibiting the activation of c-Jun N-terminal kinase (JNK) and p38 pathways in human umbilical vein endothelial cells and further suppressed the nuclear factor-kappa B (NF-κB) signaling and downregulated the expression of inflammatory factors (Zhou et al., 2017). In addition, ginsenoside Rb1 has the ability to regulate autophagy (Liu et al., 2020). It’s believed that oxidative stress, apoptosis, inflammation and autophagic dysfunction contribute to a variety of diseases, especially the central nervous system diseases (CNSDs). CNSDs, including neurodegenerative diseases, cerebral ischemia injury, depression and spinal cord injury, which are always difficult to cure clinically. Therapeutic drugs used clinically fail to block the development of diseases or are proved to produce severe side effects. Thus, there is an urgent need to develop new drugs to treat these diseases. In the last two decades, ginsenoside Rb1 is reported to play potent neuroprotection in rodent models of CNSDs. In this review, we summarize the neuroprotective roles of ginsenoside Rb1 and highlight its potential molecular mechanisms.
GINSENSIDE RB1 IN NEURODEGENERATIVE DISEASES

Alzheimer’s Disease

Alzheimer’s disease (AD) is the most common neurodegenerative disease, characterized by progressive cognitive and behavioral impairment (Mao et al., 2018). The pathological features of AD are Amyloid β (Aβ) deposition (Harrison et al., 2021), tau protein hyperphosphorylation (Xia et al., 2021) and loss of hippocampal neurons (Edler et al., 2017).

Some in vitro studies showed that ginsenoside Rb1 protected against Aβ-induced cytotoxicity in various cells (Qian et al., 2009; Xie et al., 2010). Changhong and others found that ginsenoside Rb1 treatment could serve as an activator of peroxisome proliferator-activated receptor-γ (PPARγ) and reduce the level of cholesterol and further lowered the cytotoxicity of Aβ25-35 in PC12 cells (Changhong et al., 2021). Several in vivo studies revealed the neuroprotective roles and potential mechanisms in various AD models. Oral administration of ginsenoside Rb1 significantly shortened the escape latency in the Morris water maze (MWM) test and reduced the number of errors in the passive avoidance task by decreasing protein expression levels of ASC, caspase-1 and Aβ, repairing neuronal cells loss and inhibiting the activation of astrocyte and microglia in hippocampus of SAMP8 mice (Yang et al., 2020c). More importantly, ginsenoside Rb1 was more effective than another ginsenoside, Rg1, in SAMP8 mice. One interesting study showed that ginsenoside Rb1 given orally is completely metabolized to 20-O-β-D-glucopyranosyl-20(S)-protopanaxadiol (M1) to exert neuroprotective role (Tohda et al., 2004). Ginsenoside Rb1 improved memory and cognitive ability of streptozotocin (STZ)- injected mice and also relieved glucose intolerance induced by STZ injection by enhancing insulin sensitivity (Yang et al., 2020b). These beneficial effects of ginsenoside Rb1 is most likely mediated by upregulating the expression of NMDAR1 and IDE in the hippocampus through inhibiting the activity of CDK5/p53. Ginsenoside Rb1 treatment decreased the levels of Bax and cleaved caspase-3, upregulated the level of Bcl-2 in the hippocampus (Wang et al., 2018c), suggesting that ginsenoside Rb1 inhibited Aβ1-40-induced mitochondrial apoptosis pathway.

The abnormal deposition of Aβ, a common induction pathway in AD (Hardy and Selkoe, 2002), exhibits neurotoxicity and may lead to a complex array of responses, including an inflammatory cascade (Streit, 2004). AD inflammation and thrombosis are promoted by Aβ through interaction with circulating protein XII and fibrinogen (Zamolodchikov and Strickland, 2016). Pro-inflammatory cytokines such as interleukin-1β (IL-1β), IL-6, IL-10, and TNF-β were found to have increased expression in the brain and cerebrospinal fluid of AD patients (Mrak and Griffin, 2005; Jiang et al., 2011). Interestingly, ginsenoside Rb1 mitigated the isoflurane/surgery-induced cognitive impairment- and synapse dysfunction via decreasing levels of ROS, TNF-α and IL-6 in the mice hippocampus, suggesting that the mechanisms refer to inhibiting oxidative stress and neuroinflammation (Miao et al., 2017). Glial fibrillary acidic protein (GFAP), an astrocyte marker, is associated with memory impairment and neuronal reduction (Murphy et al., 2003). In a Aβ1-40-induced AD model, the expression of inflammation-related genes Aβ, IL-1β, and GFAP were decreased in the hippocampus of rats after ginsenoside Rb1 injection (Lin et al., 2019), indicating that ginsenoside Rb1 can reduce the neuroinflammation in AD. The increased number of hippocampal neurons in CA1 area may be involved with the ability of ginsenoside Rb1 promoting the proliferation and differentiation of neural stem cells (NSC) in AD model (Zhao et al., 2018b). (Table 1).

Neurofibrillary tangles (NFTs), composed of hyperphosphorylated microtubule-associated protein tau, are a defining pathological feature of AD. It is hypothesized that hyperphosphorylation of tau impairs the microtubule-stabilizing function of tau, leading to the formation of paired helical filaments and neuronal death (Liu et al., 2003). In spite of the fact that Aβ aggregation is considered an important causative factor of AD, there are great correlations between clinical symptoms, atrophy and brain damage and the appearance of tau aggregation (Bennett et al., 2017). Ginsenoside Rb1 can reduce the expression of phosphorylated tau protein in brain slices of rat model of AD and effectively reduce the formation of NFTs (Wang et al., 2013). Overexpression of glycogen synthase kinase-3β (GSK3β), a tau protein kinase, induced hyperphosphorylation of tau protein in cellular and animal models (Lucas et al., 2001). Brain-derived neurotrophic factor (BDNF) inhibited tau protein phosphorylation by suppressing the activity of GSK3β (Liu et al., 2003). Ginsenoside Rb1 inhibits tau protein phosphorylation by upregulating BDNF and therefore has a preventive effect in AD (Wang et al., 2013). Increasing studies have shown that Aβ induced the hyperphosphorylation of tau. Ginsenoside Rb1 inhibited fibrillar Aβ25-35-induced tau hyperphosphorylation in primary cultured cortical neurons via inactivating Ca2+/calpain/CDK5 signal pathway (Chen et al., 2008) (Table 1).

Several omics researches revealed the neuroprotection of ginsenoside Rb1 in AD. An RNA sequencing study demonstrated ginsenoside Rb1 could regulate the expression of genes related to nervous system development and mitogen-activated protein kinase (MAPK) signaling pathway in SAMP8 mice (Zhang et al., 2017). Ginsenoside Rb1 treatment also showed a potential to upregulate the expression of proteins, such as CAP1, CAPZB, TOMM40, and DATN which are essential for growth cone morphology and neurite outgrowth according to results of a proteomics study (Hwang et al., 2016). In addition, a metabolomic study revealed that ginsenoside Rb1 displayed anti-AD effects through regulating lecithin and amino acid metabolism (Li et al., 2015).

These researches demonstrated that ginsenoside Rb1 have potent effects in alleviating the pathological features of AD, suggesting ginsenoside Rb1 may be a competitive candidate for AD therapy.

Parkinson Disease

Parkinson Disease (PD), one of the most common neurodegenerative diseases (Obeso et al., 2017), is characterized by the loss of dopaminergic neurons in the substantia nigra of midbrain (Zeng et al., 2014a). Actually,
increasing studies have shown that both genetic and environmental factors may lead to PD inspite of the unknown pathology of PD (Kim and Alcalay, 2017). Based on current studies, the mutations of several genes, including α-synuclein, LRRK2, PINK1, Parkin, DJ-1, VPS35, and GBA1, lead to the onset of PD (Zeng et al., 2018c). Various biological processes, such as dopamine metabolism, mitochondrial dysfunction, endoplasmic reticulum stress, impaired autophagy, and deregulation of immunity could lead to the loss of dopaminergic neurons (Zeng et al., 2018c).

Normally, pathologic changes of PD contain the appearance of Lewy bodies and the mass death of dopaminergic neurons (Simon et al., 2020). The misfolded of α-synuclein (α-syn) is a classic sign in PD. Study shows that the initial α-syn aggregations are neurotoxic since they cause the death of the cells (Mehra et al., 2019). Ardah et al. (2015) found that ginsenoside Rb1 could inhibit the toxicity and aggregation of α-syn; What’s more, ginsenoside Rb1 exhibited a strong ability to decompose preformed fibrils. Mechanistically, ginsenoside Rb1 bonds to soluble non-toxic oligomers with no β-sheet content, making it susceptible to proteinase K digestion. Ginsenoside Rb1 attenuated the lipopolysaccharide (LPS)-induced depletion of dopamine and its metabolites in the striatum, inhibiting dopamine (DA)ergic neuron degeneration in the substantial nigra via inhibiting the activation of microglia in substantial nigra by downregulating LPS-induced activation of NF-κB signaling pathway (Li et al., 2019a). An earlier study showed that ginsenoside Rb1 significantly increased the numbers and lengths of neurites of surviving DA neurons although it could not prevent cell death by glutamate challenge (Radad et al., 2004). 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is a commonly used reagent to build PD model in mice (Zeng et al., 2018b), which could cross the blood-brain barrier (BBB, acting as the gatekeeper of the CNS in maintaining the delicate homeostasis of the brain), and be metabolized into the potent dopaminergic neurotoxin 1-methyl-4-phenylpyridinium ion (MPP⁺) by monoamine oxidase B in glial cells (Langston, 2017). It was reported for the first time that ginsenoside Rb1 treatment ameliorated motor deficits, prevented DA neuron death, and suppressed the expression of α-synuclein and astroglisis in the MPTP mouse model of PD (Zhang et al., 2018). Glutamate plays a role in exciting neurons and promoting them to produce action potentials in CNS. In vivo, the appropriate level of glutamate is maintained by astrocytic glutamate transporters. However, too much endogenous glutamate may cause the death of the excitotoxic neurons, which may be connected with PD (Pajarillo et al., 2019). Zhang et al. (2018) found that ginsenoside Rb1 could suppress the excitotoxicity of glutamate by increasing glutamate transporter expression via nuclear translocation of NF-κB and modulates synaptic transmission in MPTP model of PD. In addition, ginsenoside Rb1 attenuated MPTP-induced cognitive impairment and dysfunctional gait dynamic via regulating gamma-aminobutyric acid (GABA)ergic transmission in the prefrontal cortex (PFC) (Liu et al., 2019). Administration of ginsenoside Rb1 also improved the memory deficiency of MPTP-treated mice via promoting hippocampal CA3 α-syn monomer expression, restoring the glutamate in the CA3-schaffer collateral-CA1 pathway, and sequentially increasing postsynaptic density-95 (PSD-95) expression (Qu et al., 2019) (Table 2). These researches suggest that ginsenoside Rb1 may serve as a potential therapeutic agent for PD.

**Other Neurodegenerative Diseases**

A few studies also found that ginsenoside Rb1 showed neuroprotection in other neurodegenerative diseases, such as epilepsy and Huntington’s disease (HD). Ginsenoside Rb1 ameliorated pentylenetetrazol (PTZ)-injured longer seizure duration and shorter seizure latency, as well as the cognitive deficits and neuronal damage in rats via Rb1 dose-dependently increasing GSH levels, decreasing MDA levels, and activating Nrf2/ARE signaling (Shi et al., 2018). Its metabolic production, compound K, exerted anti-epileptic effects by promoting the hippocampal release of GABA and enhancing the GABAₐ receptor-mediated inhibitory synaptic transmission (Zeng et al., 2018). Nanomolar concentrations of ginsenoside Rb1

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**TABLE 2**

| AD models                  | Dose of Rb1 | Effects                        | Mechanisms                                      | References                          |
|----------------------------|-------------|--------------------------------|-------------------------------------------------|-------------------------------------|
| Aβ25-35-treated PC12 cells | 50 μM       | Inhibiting cytotoxicity of Aβ  | Antioxidant                                     | Changhong et al. (2021)             |
| SAMP8 mice                 | 60 μmol/kg orally for 8 weeks | Improving memory and cognitive ability | Anti-neuroinflammation, inactivating astrocyte and microglia | Yujie Yang et al. (2020c) |
| STZ-injected mice          | 30 mg/kg    | Improving memory and cognitive ability | Upregulating the expression of NMDAR1 and IDE in the hippocampus | Ranyao Yang et al. (2020b) |
| Aβ1-40-treated rats        | 25 mg/kg for 14 consecutive days | Preventing cognitive deficit | Anti-apoptosis in the hippocampus | Yiru Wang et al. (2018c) |
| Aβ1-40-treated rats        | 25 mg/kg for 2 weeks | Improving learning and memory ability | Anti-neuroinflammation | Lin et al. (2019) |
| Hippocampal injection of Aβ40 | 10 mg/kg daily for 30 days | Promoting proliferation and differentiation of NSCs | N/A                                      | Jiwei Zhao et al. (2018a) |
| Okadaic acid-treated brain slice | 240 μM for 4 h | N/A                            | Suppressing tau hyperphosphorylation and upregulating BDNF expression | Wang et al. (2013) |
| Aβ25-35-treated rat cortical neurons | 40 μM for 24 h | Inhibiting cytotoxicity of Aβ | Attenuating tau hyperphosphorylation and regulating Ca²⁺ signaling | Chen et al. (2008) |
which eventually lead to neuronal apoptosis and brain tissue response, excitatory neurotransmitter release and energy failure, pathological events such as oxidative stress, neuroinflammation, and mitochondrial dysfunction. Notably, the protective effect of ginsenoside Rb1 is stronger than others in CNS diseases.

**GINSENOSIDE RB1 IN CEREBRAL ISCHEMIA**

Ischemic stroke is one of the leading causes of adult disability and death all over the world. Cerebral ischemia, caused by a significant blockage in cerebral blood flow, results in various pathological events such as oxidative stress, neuroinflammation, excitotoxicity, and mitochondrial dysfunction. The primary aim of acute stroke treatment is to rescue the ischemic penumbra or the brain tissue ischemia and maintaining the intracellular redox state. Trx plays crucial roles in reducing oxidative stress and restoring mitochondrial function, suggesting that ginsenoside Rb1 may serve as a potential clinically useful drug during the recovery stage of stroke. Nrf2 and CREB are the transcription factor of Trx-1, which upregulate Trx-1 expression under stress. Administration of ginsenoside Rb1 could upregulate the expression of neurotrophic factor, which is beneficial for the neural survival. In a rat MCAO model, injection of ginsenoside Rb1 immediately after the onset of reperfusion significantly upregulated expression of BDNF, which induced the neurogenesis and promoted the recovery of neurological functions. In addition, Ginsenoside Rb1 also significantly increased the expression of nerve growth factor (NGF) and BDNF, as well as the expression of aquaporin 4 (AQP4), in OGD/R-induced rat astrocytes (Li et al., 2019b).

Increasing studies have suggested that neuroinflammation play an important role in the pathology of stroke. The main aim of acute stroke treatment is to rescue the ischemic penumbra or nonfunctional, yet still viable tissue surrounding the infarcted core. During ischemic stroke, the integrity of BBB tight junctions can be seriously destroyed due to blocked or reduced circulating blood flow. Ginsenoside Rb1 protects loss of BBB integrity in ischemic stroke by suppressing neuroinflammation induction of matrix metalloproteinase-9 (MMP-9) and nicotinamide adenine dinucleotide phosphate oxidase 4 (NOX4)-derived free radical. A study reported that ginsenoside Rb1 administration markedly mitigated the activation of microglia in the ischemic penumbra by inhibiting the expression of TNF-α and IL-6 and the activation of NF-κB (Zhu et al., 2012), suggesting that ginsenoside Rb1 treatment is beneficial for salvaging the ischemic penumbra via inhibiting microglia-mediated neuroinflammation. High-mobility group box 1 (HMGB1) is released after focal cerebral ischemia, and HMGB1 is involved in the regulation of microglia activation and neuroinflammation.

**TABLE 2 | The neuroprotection of ginsenoside Rb1 in PD.**

| PD models | Dose of Rb1 | Effects | Mechanisms | References |
|-----------|-------------|---------|------------|------------|
| α-syn-treated BE(2)-M17 cells | 5 μM | Restoring the decreased cell viability | Inhibiting α-syn fibrillation and toxicity | Ardah et al. (2015) |
| LPS-induced rat model | 20 mg/kg for 14 consecutive days | Restoring DA and its metabolites in striatum and DA neurons degeneration in SN | Inactivating microglia in SN and inhibiting neuroinflammation | Da-Wei Li et al. (2019a) |
| MPTP-induced mouse model | 40 mg/kg for 14 consecutive days | Ameliorating motor deficits, preventing DA neuron death | Attenuating glutamate excitotoxicity and modulating glutamatergic transmission pathways | Zhang et al. (2018) |
| MPTP-induced mouse model | 10 mg/kg for 14 consecutive days | Mitigating MPTP-induced altered gait parameters and cognitive impairment | Regulating GABAergic transmission | Liu et al. (2019) |
| MPTP-induced mouse model | 40 mg/kg for 14 consecutive days, starting 3 days before MPTP treatment | Improving memory deficiency | Improving synaptic plasticity | Qu et al. (2019) |

Ginsenoside Rb1 effectively protected YAC128 medium spiny striatal neurons from YAC128 HD model mice against glutamate-induced apoptosis and Ca²⁺ responses (Wu et al., 2009). Notably, the protective effect of ginsenoside Rb1 is stronger than others ginsenosides.

**TABLE 3**

| Parameters | MPTP-induced model | Restoring the decreased cell viability | Mitigating MPTP-induced altered gait parameters and cognitive impairment | Improving memory deficiency | Improving synaptic plasticity |
|------------|---------------------|--------------------------------------|-----------------------------------------------|-------------------------------|------------------------------|
| MPTP-induced model | 10 mg/kg for 14 consecutive days | Improving memory deficiency | Improving synaptic plasticity | | |
| MPTP-induced model | 40 mg/kg for 14 consecutive days | Restoring the decreased cell viability | Mitigating MPTP-induced altered gait parameters and cognitive impairment | Improving memory deficiency | Improving synaptic plasticity |
| MPTP-induced model | 10 mg/kg for 14 consecutive days | Improving memory deficiency | Improving synaptic plasticity | | |
| MPTP-induced model | 40 mg/kg for 14 consecutive days | Restoring the decreased cell viability | Mitigating MPTP-induced altered gait parameters and cognitive impairment | Improving memory deficiency | Improving synaptic plasticity |
| MPTP-induced model | 10 mg/kg for 14 consecutive days | Improving memory deficiency | Improving synaptic plasticity | | |
I/R and aggravates brain tissue damage. Ginsenoside Rb1 treatment significantly inhibited the release of HMGB1 in MCAO rats, accompanied by decreasing the levels of NF-κB, TNFα, IL-6, and inducible nitric oxide synthase (iNOS) (Liu et al., 2018a), suggesting that the effects of ginsenoside Rb1 may be associated with the inhibition of HMGB1 inflammatory signals (Table 3).

The function of ginsenoside Rb1 in cerebral ischemia is related to common pro-survival pathways in cells. Ginsenoside Rb1 treatment upregulated the protein level of p-Akt at Ser473 and inhibited the elevation in protein levels of LC3II and Beclin1 and protected against OGD and transient global ischemia (two vessels occlusion)-induced injury (Luo et al., 2014). The recovery of brain damage after MCAO is significantly impaired in aged mice compared with young mice. Interestingly, long-term oral administration of ginsenoside Rb1 greatly prevented the injury in a dose-dependent manner by inhibiting oxidative stress and the activation of extracellular signal-regulated kinase 1/2 (ERK1/2) in aged mice (Dong et al., 2017). ERK1/2 activation is also a well-known pro-survival pathway, signal-regulated kinase 1/2 (ERK1/2) in aged mice (Dong et al., 2017). ERK1/2 activation is also a well-known pro-survival pathway, signal-regulated kinase 1/2 (ERK1/2) in aged mice (Dong et al., 2017).

These researches suggest that ginsenoside Rb1 may serve as a potential therapeutic agent for cerebral ischemia.

### GINSENSOIDE RB1 IN DEPRESSION

Depression, a common psychiatric disease and the leading cause of disability worldwide (Lopez and Murray, 1998), is a heterogenous diagnostic concept consisting of a set of different symptoms, with decreased mood, anhedonia, and reduced energy defined as core symptomatologies in ICD-10 and depressed mood and loss of interest and pleasure in DSM-5 (Hoflich et al., 2019). Depression is often associated with chronic illnesses (Evans et al., 2005) or other mood disorders such as co-morbid anxiety (Menard et al., 2016). At present, it is generally believed that dysfunction of monoamine neurotransmitters and their receptors, decrease in neurotrophic factors, neuroinflammation, activity enhancement of HPA axis are involved in the pathogenesis of depression. Monoamine oxidase inhibitors (MAOI), selective serotonin reuptake inhibitors (SSRI) or serotonin norepinephrine reuptake inhibitors (SNRI) are used clinically to treat moderate to severe depression (Walker, 2013). Unfortunately, these inhibitors are well recognized to produce a number of undesirable side effects that often lead to patient noncompliance. With the in-depth study of traditional Chinese medicine, people began to seek active ingredients from natural products for the treatment of depression. Increasing evidence demonstrated that ginsenoside Rb1 could significantly improve the depressive-like behaviors in various rodent models.

In a lipopolysaccharide (LPS)-induced depressive model, ginsenoside Rb1 significantly suppressed peripheral and hippocampal inflammation via MAPK/NF-κB signaling, improved impaired glucocorticoid receptor and inhibited activity of indoleamine 2,3-dioxygenase (Liang et al., 2022). The authors also found that ginsenoside Rb1 increased the levels of 5-HT and expression of 5-HT1A receptor. The treatment with 5-HT1A receptor antagonist, NAN190 or 5-HT2A receptor antagonist, ritanserin, reversed the antidepressant-like effect of ginsenoside Rb1 in chronic unpredictable mild stress (CUMS) mice (Yamada et al., 2011; Wang et al., 2018a), suggesting that serotonergic receptor may be involved in the antidepressant-like effect of ginsenoside Rb1. Besides, dopaminergic and noradrenergic systems are also involved in the antidepressant-like effects of ginsenoside Rb1 (Wang et al., 2017). Rd, F2, compound K, Rh2, and Rg3 were
identified as the metabolites of ginsenoside Rb1. Liang et al. (2022) found that F2 exerted antidepressant-like effects and it showed higher activity than ginsenoside Rb1 against depression (Table 4).

Ginsenoside Rb1 exerted promising antidepressant-like effects in mice with chronic social defeat stress (CSDS)-induced depression by enhancing the BDNF/TrkB signaling pathway, which increased the hippocampal neurogenesis (Jiang et al., 2021a). Similarly, ginsenoside Rb1 treatment ameliorated chronic restraint stress (CRS)-induced memory impairments in rats by improving synaptic plasticity and restoring the BDNF/TrkB signalling pathway (Jiang et al., 2021b). Guo et al. (2021) found that ginsenoside Rb1 not only increased the protein expression of BDNF, but also activated the pro-survival Akt pathway in CRS mice. In addition, ginsenoside Rb1 alleviated the inflammation induced by CRS, including decrease in the protein expression of IL-1β, TNF-α and ionized calcium binding adapter molecule 1 in hippocampus, and reduce in the levels of IL-1β and TNF-α in serum (Guo et al., 2021). Intervention with ginsenoside Rb1 for 2 weeks induced a pro-neurogenic phenotype of microglia via activating peroxisome proliferator-activated receptor y (PPARγ), inhibited chronic mild stress (CMS)-induced inflammation and increased the proliferation and differentiation of neural precursor cells (Zhang et al., 2021) (Table 4).

These studies have demonstrated that ginsenoside Rb1 could improve the depressive-like behaviors through regulating the balance of neurotransmitters, inhibiting the neuroinflammation and promoting neuronal survival. Thus, ginsenoside Rb1 may be a promising candidate in the therapy of depression.

**GINSENOSIDE RB1 IN SPINAL CORD INJURY**

Spinal cord, located in the spinal canal, is one part of the central nervous system. The spinal cord is comprised of white matter and gray matter, which includes cerebral nuclei and fiber conduction bundle. Spinal cord injury (SCI) is a central nervous system disease, which is classified as traumatic SCI (TSCI) and non-traumatic SCI (NTSCI), and this disease can lead to the permanent disability (Gedde et al., 2019). Currently, the prevalence of SCI witnesses a rise which makes a burden to the individual and the society because it is still incurable (Ahuja et al., 2017b). Since the functions of the spinal cord contain the motor adjustment and the sensory transmission, the position and the degree about SCI have different effect on the consequences. The causes of TSCI contain recreational activities, violence falls, traffic accident and so on (McDonald and Sadowsky, 2002) and that of NTSCI include compression of tumor, spinal canal stenosis, vascular ischemia, inflammatory conditions and so on (New and Sundararajan, 2008). Broadly speaking, the treatments of SCI contain neuroprotection and nerve regeneration (Kim et al., 2017). At present, the clinical treatment of SCI includes surgical decompression, drug therapy and early definitive care and so on (Ahuja et al., 2017a). Recently, more and more researches showed that ginsenoside Rb1 may have fine effects on the recovery of SCI.

Wang and others found that in SCI rats ginsenoside Rb1 treatment facilitated the expression of miR-130b-5p, which inactivated Toll-like receptor 4 (TLR4)/NF-κB in microglia and further increased Basso, Beattie, and Bresnahan score (BBBs) and reduced TUNEL-positive cell proportion and inflammation (Wang et al., 2021), suggesting that ginsenoside Rb1 alleviated SCI through reducing activated microglia-induced neuronal injury via miR-130b-5p/TLR4/NF-κB axis. Administration of ginsenoside Rb1 also significantly inhibited oxidative stress, including decreasing serum MDA content and increasing the activity of SOD, CAT and GSH, at least partly via the eNOS/Nrf2/HO-1 pathway in SCI rats, and improved spinal cord function score (Liu et al., 2018b). Ginsenoside Rb1 could improve neurological function of hind limbs and reduce the cell apoptosis through decreasing MDA content in serum and spinal cord tissue and increasing activity of SOD, as well as inhibit apoptosis by promoting the expression of Survivin protein in spinal cord I/R injury (SCI) rats (Ye et al., 2019). Importantly, Zhao et al., 2018a found that ginsenoside Rb1 injection after surgical operation also prevented neural cell apoptosis in the spinal cord and improved hindlimb locomotor dysfunction of

**TABLE 4 | The neuroprotection of ginsenoside Rb1 in depression.**

| Models                        | Dose of Rb1 | Effects                                      | Mechanisms                              | References                  |
|-------------------------------|-------------|----------------------------------------------|------------------------------------------|-----------------------------|
| LPS-induced depressive mice   | 10–20 mg/kg daily for 11 consecutive days | Ameliorating LPS-induced depressive-like behaviors | Anti-inflammation, improving impaired inflammatory response | Liang et al. (2022) |
| CUMS mice                     | 5–20 mg/kg for 7 days | Decreasing the immobility time in the FST | Glucocorticoid receptor | Guo et al. (2018b) |
| CUMS mice                     | 4–10 mg/kg for 21 days | Decreasing immobility time in the FST and TST | Balancing neurotransmitters and decreasing the level of Glu | Yamada et al. (2011) |
| CSDS mice                     | 35–70 mg/kg daily orally for 28 days | Reversing the social avoidance behavior, anhedonia, and behavioral despair | Enhancing the BDNF signaling and upregulating hippocampal neurogenesis | Jiang et al. (2021a) |
| CRS rats                      | 6.75–13.5 mg/kg | Ameliorating the memory impairments | Antioxidant; anti-apoptosis; improving synaptic plasticity; restoring the BDNF signaling | Jiang et al. (2021b) |
| CRS mice                      | 10 mg/kg by intraperitoneal injection for 14 days | Relieving the depression-like behaviors | Anti-inflammation; pro-survival; increasing BDNF expression | Guo et al. (2021) |
| CMS-exposed mice              | 20 mg/kg for 4 weeks | Ameliorating depressive-like behaviors | Inducing a pro-neurogenic phenotype of microglia, anti-inflammation | Zhang et al. (2021) |
SCII rats via inhibiting the activation of caspase-3 and apoptosis signal-regulating kinase (ASK 1), and the Bax/Bcl-2 ratio, suggesting that ginsenoside Rb1 may be a potential drug for SCII treatment. Sakanaka et al. (2007) produced dihydroginsenoside Rb1 and found that its effective dose to improve SCI was ten times lower than that of ginsenoside Rb1. Dihydroginsenoside Rb1 rescued SCI-induced neuronal damage through upregulating the expression of Bcl-x(L) and vascular endothelial growth factor (VEGF) by activating hypoxia response element (HRE) and signal transducers and activators of transcription 5 (Stat5), respectively. (Table 5).

Demyelination occurs after SCI due to the injury and the imbalance of the microenvironment while myelin promotes facilitate axon signal conduction. Study shows that the unceasing loss of oligodendrocytes may lead to the barrier to the function recovery, while the reason why the loss of oligodendrocytes happens owes to the imbalance between the remyelination and the demyelination (Fan et al., 2018). Ginsenoside compound K, a metabolite of ginsenoside Rb1, promoted the proliferation, migration and differentiation of Schwann cells, which are critical for the remyelination of injured peripheral nerve, via activating MEK/ERK1/2 and

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### TABLE 5 | The neuroprotection of ginsenoside Rb1 in SCI.

| Models          | Dose of Rb1                        | Effects                                                                 | Mechanisms                                                                                      | References                  |
|-----------------|------------------------------------|------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|-----------------------------|
| SCI rats        | 40 mg/kg at 30 min and 24 h after SCI treatment | Increasing BBBs and reducing TUNEL positive cell proportion            | Inactivating microglia; anti-inflammatory                                                         | Dan Wang et al. (2021a)     |
| SCI rats        | 10 mg/kg at 30 min after modeling and then daily for 7 days | Improving spinal cord function score                                    | Anti-oxidant; anti-inflammation                                                                | Xinwei Liu et al. (2018b)  |
| SCII rats       | 10–80 mg/kg 30 min before SCII and the same do as before every day until being sacrificed | Improving neurological function of hind limbs                           | Anti-oxidant; anti-apoptosis; increasing survivin protein expression                           | Ye et al. (2019)            |
| SCII rats       | 10 mg/kg after SCII model for 7 days  | Improving hindlimb locomotor dysfunction of rats                       | Anti-apoptosis                                                                                   | Dongxu Zhao et al. (2018a) |
| SCII rats       | 1.2–6 μg/day of dihydroginsenoside Rb1 intravenously infused | Rescuing damaged neurons in spinal cord                                | Anti-apoptosis and upregulating VEGF expression                                                  | Sakanaka et al. (2007)     |
| SCI rats        | 20 mg/kg for 2 weeks               | Decreasing the loss of motor neurons, promoting function recovery      | Anti-apoptosis                                                                                   | Peng Wang et al. (2018b)   |

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FIGURE 2 | Protective mechanisms of ginsenoside Rb1 in CNSDs.
P38K/Akt pathways (Wang et al., 2021). Autophagy is the process of engulfing unwanted cells and maintaining homeostasis. A study shows that autophagy may lead to the death of the oligodendrocytes while functional recovery requires the participation of oligodendrocytes (Fan et al., 2018). The maintenance of neurons requires the participation of autophagy. However, high levels of autophagy may lead to neuronal cell death and further cause neurodegeneration. Bisicchia and his others demonstrated that inhibition of autophagy improved the survival rate of rats with spinal cord hemisection (Bisicchia et al., 2017). Wang et al. (2018b) found ginsenoside Rb1 treatment decreased the death of motor neurons and promoted the recovery of motor function, as well as restored the expression of LC3-II/I, Beclin-1, and p62 in the SCI rats, suggesting that ginsenoside Rb1 may play neuroprotective role via inhibiting autophagy and autophagic cell death. (Table 5). These data suggest that ginsenoside Rb1 may be a promising candidate in the therapy of SCI.

CONCLUSION AND EXPECTATION

In summary, current studies have demonstrated that ginsenoside Rb1 exerts neuroprotective roles through inhibiting oxidative stress, apoptosis and neuroinflammation and regulating the autophagy in neurodegenerative diseases, cerebral ischemia injury, depression and spinal cord injury (Figure 2). More importantly, the effects of ginsenoside Rb1 seems to be much stronger than other ginsenosides, suggesting that may be a promising candidate agent for clinical therapy of CNSDs.

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At this stage, the associated studies are extremely few and limited to focus on the neuroprotective effects of ginsenoside Rb1 in CNSDs in cellular and rodent models. The experiments in nonhuman primate models of CNSDs and the clinical trials should be also successively carried out to accelerate the clinical application of ginsenoside Rb1 for CNSDs treatment in the future. There are different routes of administration and the dosage used in rodents is in a large range. Further studies are also needed to performed to confirm the optimal administration route and dosage for individual disease.

AUTHOR CONTRIBUTIONS

XZ and JJ designed the article contents. LG, JY, YZ, RH, and HJ wrote the original paper. YL and XZ drew the figure. XZ, JJ, and LS revised the paper. All authors reviewed the paper and approved the submitted version.

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