Pharmacological activities, mechanisms of action, and safety of salidroside in the central nervous system

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Abstract: The primary objective of this review article was to summarize comprehensive information related to the neuropharmacological activity, mechanisms of action, toxicity, and safety of salidroside in medicine. A number of studies have revealed that salidroside exhibits neuroprotective activities, including anti-Alzheimer’s disease, anti-Parkinson’s disease, anti-Huntington’s disease, anti-stroke, anti-depressive effects, and anti-traumatic brain injury; it is also useful for improving cognitive function, treating addiction, and preventing epilepsy. The mechanisms underlying the potential protective effects of salidroside involvement are the regulation of oxidative stress response, inflammation, apoptosis, hypothalamus-pituitary-adrenal axis, neurotransmission, neural regeneration, and the cholinergic system. Being free of side effects makes salidroside potentially attractive as a candidate drug for the treatment of neurological disorders. It is evident from the available published literature that salidroside has potential use as a beneficial therapeutic medicine with high efficacy and low toxicity to the central nervous system. However, the definite target protein molecules remain unclear, and clinical trials regarding this are currently insufficient; thus, guidance for further research on the molecular mechanisms and clinical applications of salidroside is urgent.

Keywords: salidroside, Alzheimer’s disease, Parkinson’s disease, stroke, cognitive impairment, clinical trials

Introduction

Rhodiola rosea L., a small genus of the Crassulaceae family, has a long history of wide use as a botanical medicine in Europe, Asia, and the US to prevent and treat a great variety of common conditions and complex diseases, including fatigue, various pains, Alzheimer’s disease (AD), depression, and anxiety.¹,² It is also used as an adaptogen and cardiopulmonary protective agent in traditional folk medicine.³ Rhodiola rosea extracts contain about 1% salidroside (Figure 1).⁴ The salidroside content contributes a lot to the properties of Rhodiola, and is the main active bioactive component in Rhodiola rosea. Salidroside has also been found in other species.⁵⁻¹⁰ Meanwhile, the chemical and biological synthesis of salidroside have been investigated in various studies.¹¹⁻¹⁶

In pharmacokinetics, p-tirosol (aglycone of salidroside) has been identified as a metabolite in the plasma of rats treated with salidroside, and salidroside was detected in brain tissue.¹⁷⁻¹⁹ Some studies have reported that salidroside has various pharmacological effects, such as an anti-AD, anti-PD, anti-stroke, anti-Huntington’s disease (HD), anti-TBI, anti-depressive, anti-cancer, anti-coxsackie, rejuvenating, anti-diabetes, cardioprotective, vasculoprotective, and hepatoprotective effects, as...
well as improves cognitive function, treats addiction, and prevents epilepsy across a wide therapeutic time window.\textsuperscript{19–32}

Recently, an increasing number of studies have been conducted on the neuroprotective effects of salidroside (Figure 2); however, neither in vivo nor in vitro experiments have been thoroughly studied. This review will systematically summarize and comprehensively analyze the developments and adaptogenic mechanisms of action in the neuropharmacological study of salidroside (Table 1; Figure 3), and provide suggestions for further studies.

**Pharmacological activity and mechanisms of action**

**Anti-Alzheimer’s disease effect**

AD, the most common progressive neurodegenerative disorder, is clinically characterized by cognitive impairment, memory dysfunction, and behavioral disorder in the elderly. AD affects approximately 36 million people worldwide, and this number is expected to nearly double over the next 20 years.\textsuperscript{33,34} Drug treatment is the most commonly used option for the disease. At present, only a small number of drugs have been approved in clinical practice, such as donepezil, rivastigmine, galantamine, memantine, and the Chinese herb extract huperzine A.\textsuperscript{35,36} Additional traditional Chinese medicine studies have shown that salidroside exerts promising effects in the treatment of AD.

In recent years, an increasing body of evidence has suggested that Aβ plays an important role in neuronal dysfunction and cellular death.\textsuperscript{37} Thus, Aβ-induced disease is an important research focus for examining AD onset and progression. An in vitro study in Aβ\textsubscript{1–42}-induced AD PC12 cell lines determined that salidroside reduced cytotoxicity, attenuated reactive oxygen species (ROS) accumulation, and decreased intracellular malondialdehyde by activating antioxidant enzymes in a dose-dependent manner after 3 h pre-incubation with salidroside (1, 5, 10, and 50 mg/mL).\textsuperscript{38} Furthermore, pretreatment with salidroside (10, 50, and 100 µM) was shown to significantly inhibit oxidative stress and apoptosis in Aβ\textsubscript{25–35}-induced SH-SY5Y cells in a concentration-dependent manner in vitro via increasing antioxidant enzyme activities, modulating apoptosis-related protein expression, and restoring anomalies in the mitochondrial membrane potential (MMP) and ROS production.\textsuperscript{39} In addition, it was found that salidroside (5, 100, and 200 µM) decreased Aβ levels in Aβ\textsubscript{1–42}-incubated primary neurons via PI3K/Akt/mTOR signaling.\textsuperscript{40} Salidroside (2, 6, and 20 µM) also improved both the longevity and locomotor activity of Tao transgenic Drosophila in a dose-dependent manner. These studies revealed that the protective effects of salidroside were due to the up-regulation of total p-GSK3β and down-regulation of p-tau.\textsuperscript{40,41}

Apart from the Aβ-induced AD model, streptozotocin (STZ), D-galactose, glutamate, H\textsubscript{2}O\textsubscript{2}, and hypoxia are also used to mimic AD in studies. A previous study revealed that direct incubation with salidroside (1 mM) exhibited neuroprotective effects on active neural stem cells (NSCs)
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Salidroside in the central nervous system

Anti-Parkinson’s disease effect

Parkinson’s disease (PD) is the second most common neurodegenerative disorder after AD, and affects about 1%–2% of the population over 65 years of age. As a movement disorder, the clinical symptoms of PD include static tremor, rigidity, bradykinesia, and postural instability. L-DOPA is the most effective symptomatic therapy for PD. However, long-term administration of L-DOPA currently causes severe side effects, which has prompted the search of new substitutes for anti-PD treatment.

Li et al and Zhang et al have made notable contributions on the anti-PD effect of salidroside. In their previous studies, salidroside (1–100 µM) was reported to inhibit apoptosis, as well as to attenuate MMP collapse, chromatin condensation, and the release of lactate dehydrogenase, induced by MPP⁺ (500 µM) in PC12 cells via NO and the PI3K/Akt pathway. A further study indicated that pretreatment with salidroside (15 and 45 mg/kg) improved behavior disorders in an MPTP-induced PD mouse model when administered once a day for 7 consecutive days. In these studies, salidroside ameliorated tyrosine hydroxylase-positive neuron loss in SNpc by increasing monoamine substances levels, and the neuroprotection observed may be related to the PI3K/Akt/GSK3β and ROS-NO-related pathways.

Notes:
- Upward arrows (↑) denote increase, downregulation, or suppression.
- Abbreviations: β-site APP cleaving enzyme; BDNF, brain-derived neurotrophic factor; CReB, cAMP response element binding protein; CPP, conditioned place preference; cyt c, cytochrome c; DAPT, N-[N-(3,5-difluorophenacetyl)-l-alanyl]-S-phenylglycine t-butylerester; eGCG, epigallocatechin gallate; ePM, elevated plus maze; HD, Huntington’s disease; HiF-1α, hypoxia inducible factor 1α; HPA, hypothalamus-pituitary-adrenal; iCR, institute of Cancer Research; iG, intragastrically; iP, intraperitoneally; i/R, ischemia–reperfusion; iv, intravenous; LPS, lipopolysaccharide; MADP, N-((2R,3R,4R,5S,6R)-4,5-dihydroxy-6-(hydroxymethyl)-2-(4-methoxyphenethoxy)tetrahydro-2H-pyran-3-yl)acetamide; MCAO, middle cerebral artery occlusion; MMP, mitochondrial membrane potential; MPTP, 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine; MSCs, mesenchymal stem cells; mTOR, mammalian target of rapamycin; N/A, not available/applicable; NF-κB, nuclear factor κB; Nrf2, nuclear factor erythroid 2-related factor 2; NSCs, neural stem cells; OFT, open field test; PO, per os; PD, Parkinson’s disease; pIRA, phosphorylation of insulin receptor subunit A; REDD1, regulated in development and DNA damage response 1; ROS, reactive oxygen species; SD, Sprague-Dawley; STZ, streptozocin; TBi, traumatic brain injury; TH, tyrosine hydroxylase; TNF-α, tumor necrosis factor-α.

Salidroside in STZ-induced AD rats by scavenging ROS, improving the proliferation and differentiation of NSCs in vitro. In a recent study, Gao et al showed that salidroside ameliorated D-galactose-induced cognitive deficits in rats with the administration of salidroside (20 and 40 mg/kg) once per day for 28 days. It was reported that the mechanism involved in this effect was closely connected with anti-neuroinflammation and apoptosis though mediating inflammatory cytokine levels and apoptosis factors via the SIRT1/NF-κB pathway. Moreover, salidroside inhibited the excessive increase of Ca²⁺ and release of calcium stores in PC12 cells caused by glutamate excitotoxic damage at a dose of 10⁻², 10⁻⁶, and 10⁻⁸ mol/L. A further study reported that salidroside (120 and 240 µM) also protected primary hippocampal neurons against glutamate-induced apoptosis via stimulating p-Akt in vitro. Another study reported that salidroside (1–100 µM) regulated MMP, suppressed mitochondrial cyt c release into cytosol, and attenuated caspase activation via an apoptosis pathway in H₂O₂-induced PC12 cells. Notably, salidroside (200 µM) effectively suppressed BACE1 expression, Aβ generation, and β-secretase activity, and triggered soluble amyloid precursor protein secretion in hypoxia-induced SH-SY5Y cells, suggesting that salidroside may be useful in the prevention and treatment of AD.
More recently, salidroside (25–100 µM) was also reported to significantly reduce MPP⁺-induced neuronal injury via DJ-1-Nrf2 antioxidant pathway in SH-SY5Y cells.53 Besides, it was demonstrated that salidroside (100 µg/mL) could induce the differentiation of rat mesenchymal stem cells (MSCs) to dopaminergic neurons with increased DA release.54 Salidroside was also reported to protect primary cortical neurons and SN4741 cells from endoplasmic reticulum (ER) stress.55

**Anti-stroke effect**

Stroke is currently the second most common cause of mortality in clinical practice and the third most common cause of disability worldwide, as reported in 2010.56,57 To date, tissue-type plasminogen activator is the only drug approved by the US Food and Drug Administration for the treatment of ischemic stroke.58 However, this agent is limited by a narrow therapeutic time window of time and side effects.59 Therefore, new neuroprotective agents for this devastating disease are urgently needed.

Zou et al60 initially showed that salidroside-pretreatment had neuroprotective effects on global cerebral ischemia-reperfusion rats. In this study, salidroside improved neurological severity scores and reduced the degree of cerebral edema at a dose of 12 mg/kg, whereas the underlying mechanism of action was a possible contribution to free radical scavenging. More recently, it was also reported that salidroside reduced brain edema in focal cerebral ischemia-reperfusion rats with repeated administration of salidroside at a dose of 24 mg/kg for 7 days by suppressing TNF-α release.61 Furthermore, salidroside treatment (12 mg/kg) once daily for 7 consecutive days before middle cerebral artery occlusion (MCAO) surgery markedly ameliorated neurological scores, and reduced the infarction volume and edema volume in the brain by reversing the decreased normal cells in the hippocampus and the prefrontal cortex.62 These results are in agreement with the findings of our team, reporting that salidroside exhibited a relatively strong neuroprotective action against MCAO-induced cerebral ischemia injury, as observed by the neurological deficit scores and infarct area, with administration once daily for 1 day, 2 days, and 6 days (50 mg/kg, beginning treatment at 1 h after the operation), or twice (15 and 30 mg/kg, once immediately before cerebral ischemia and once after reperfusion) administration, the underlying mechanisms were due to inhibition of apoptosis (inducing apoptosis)}
the expression of Egrs proteins) and complement drives in Egrs, while salidroside was also related with the activation of the Nrf2/antioxidant response element. In a recent study, salidroside (7.5, 20, and 40 mg/kg, or 5–20 µM) significantly inhibited RIP140/nuclear factor (NF)κB-mediated inflammation and apoptosis by reducing the protein expression ratio of Bax/Bcl-2, and downregulating inflammatory cytokine levels in MCAO rats or I/R injury-caused SH-SY5Y cells; interestingly, the neuroprotective effects of salidroside were comparable with clopidogrel (10 µM) on cerebral ischemia, both in vivo and in vitro.65

Salidroside had potential applications in cerebral ischemic disease as reported in H2O2, CoCl2, glutamate, lipopolysaccharide (LPS), hypoglycemia, glucose, and serum depletion-induced cell models in vitro. A previous study suggested that salidroside exhibited notable neuroprotective actions against H2O2-induced apoptosis and necrosis by antioxidant activities in primary cultured rat cortical neurons.62 Besides, our team further investigated the use of CoCl2-induced hypoxia damage in PC12 cells, showing that the effect of salidroside involved both the mTOR signaling pathway and Bax/Bcl-xL-related apoptosis though the induction of Egrs in vitro.66 Salidroside (120, 240, and 480 µM) also dose-dependently inhibited the CoCl2-induced primary cultured cortical neuron apoptosis by enhancing HIF-1α expression, alleviating ROS level increase and inhibiting NF-κB protein, respectively.67 Furthermore, our team found that salidroside (70–300 µM) regulated LPS-induced migration in BV2 cells by activating NF-κB, blocking p-MAPK levels (JNK, p38, and ERK1/2), and degrading tropomyosin-related kinase B (1kBz).68 In addition, several studies suggested that salidroside (20–320 µg/mL) had potential applications in cerebral ischemic disease in hypoglycemia, glucose, and serum depletion-induced models in PC12 cells in a dose-dependent manner.69–71 The protective functions of salidroside were mainly related to the attenuation of cytotoxicity by the inhibition of apoptosis and intracellular ROS production, as well as the restoration of MMP.69–71

Cognition enhancement

Learning and memory play an important role in intelligence, while learning and memory impairment is a frequent symptom of attention deficit hyperactivity disorder and fatigue in childhood and adolescent chorea. Such deficits not only negatively affect the patients’ quality of life, but are also a heavy burden to society. In recent years, various natural products have been applied for the intervention of these symptoms.72–74

It was demonstrated that phosphorylation of insulin receptor subunit A (pIRA) and SIRT1 cooperated to improve cognitive function by mitochondrial biogenesis with repeated administration of salidroside (25 mg/kg) in hypoxic rats.75 Salidroside has also shown protective effects in behavior tests and hippocampal long-term potentiation tests in rats with cognitive deficits caused by chronic cerebral hypoperfusion, by inhibiting apoptosis with administration of salidroside (20 mg/kg) once a day for 34 consecutive days.75 These observations were in line with the findings of another study demonstrating that salidroside was effective against learning and memory impairment by stimulating neurogenesis via cAMP response element binding protein (CREB) in the dentate gyrus of aging mice.76 A further study showed that oral administration of salidroside ameliorated arthritis-induced cognition dysfunction at a dose of 20 and 40 mg/kg for a consecutive 2 weeks, as observed using a Morris water maze test. According to this study, salidroside significantly decreased pro-inflammatory cytokines though the Rho/ROCK/NF-κB signaling pathway.77 These results were similar to another study reporting that salidroside exerted a protective effect against isoflurane-induced cognitive impairment in behavioral tests when administered at the doses of 60, 120, and 180 mg/kg, and it was suggested that the underlying mechanism of the effect of salidroside was related to inhibition of excessive inflammatory response, decrease of oxidative stress, and regulation of the cholinergic system.77 Additionally, salidroside (50 and 75 mg/kg) administered once per day for 21 days markedly improved the learning and memory performance in a Aβ1–42-injected AD rat model via exerting anti-oxidative and anti-inflammatory properties.78 Furthermore, the ameliorating effect of salidroside (20 and 40 mg/kg for 28 days) on cognitive function may be related to inflammatory cytokines and the SIRT1/NF-κB signaling pathway.79

Anti-depressive and anxiolytic effects

Depression is a serious and common mental disorder characterized by a persistent and prevalent depressed mood.80 According to the World Health Organization, depression is currently the fourth most common cause of morbidity and the second common cause of disability worldwide.81–83 Depression also tremendously increases the risk of suicide attempts and suicide.84 Pharmacotherapy remains at the core of treatment for depression. Although various antidepressants are currently available for the treatment of this disorder, the majority of these agents take a long time to take into full effect, while many of these usually result in co-morbid symptoms and a poor tolerance.80 Therefore, there is a clear
need for new targets and a therapeutic candidate with higher efficacy and lower toxicity.

It was reported that chronic treatment with salidroside (20 and 40 mg/kg) exhibited an antidepressant-like activity in olfactory bulbectomized rats in behavior tests, and that salidroside activity was comparable with that of amitriptyline (10 mg/kg).26 This previous study also demonstrated that the antidepressant-like effect of salidroside might be correlated to its anti-inflammatory effects and the regulation of hypothalamus-pituitary-adrenal (HPA) axis activity by reversing ER abnormalities.26 Similarly, salidroside was also reported to affect depression-like behaviors in LPS-induced mice at a dose of 12 and 24 mg/kg once daily for 5 consecutive days, and the results also indicated that the antidepressant mechanism of salidroside was related to brain-derived neurotrophic factor/tropomyosin-related kinase B (BDNF/TrkB) signaling through increasing neurotransmitters and decreasing pro-inflammatory cytokines.85 More importantly, Palmeri et al86 observed that acute administration of salidroside (25 mg/kg) exhibited antidepressant and anxiolytic effects with a high therapeutic efficacy and a low spectrum of adverse effects in mice.

Amelioration of traumatic brain injury
Salidroside treatment also led to better behavior performance in contusion-induced traumatic brain injury (TBI) in mice at a dose of 20 and 50 mg/kg by suppressing PI3K/Akt signaling pathway-mediated apoptosis.22 Furthermore, it was evidenced that salidroside (5–100 μg/mL) promoted the differentiation of MSCs D1 cells through mediating the Notch and BMP signaling pathway.87

Anti-Huntington’s disease effect
In N2, HA759, and AM141 nematodes, Xiao et al83 observed that salidroside (50–200 μM) exhibited a neuroprotective effect via the oxidative stress pathway against polyQ toxicity, suggesting that salidroside could serve as a useful anti-HD agent.

Anti-addiction effect
It was reported that treatment of male CD-1 mice with 0.2 mg/kg salidroside lowered the rewarding properties and prevented relapse to nicotine.23 These findings provide experimental foundation for further research on salidroside as a drug for withdrawal from nicotine addiction.

Anti-epileptic effect
Si et al31 researched the effect of salidroside (25 and 50 mg/kg) on kainic acid-induced SE in C57BL/6 mice, and found that salidroside pretreatment only once significantly increased the latency to epileptic and reduced the incidence of epileptic via suppressing oxidative stress. Furthermore, the AMPK/SIRT1/FoxO1 signaling pathway is possibly activated by salidroside.

Safety
Salidroside is commonly considered to be a safe and effective substance. It has been concluded that salidroside does not result in maternal or embryonic toxicity, and there are no teratogenic effects under the experimental conditions at a dose of 0.5, 0.25, and 0.125 g/kg in SD rats.84 Genotoxicity evaluation is essential in the risk assessment of drugs. The results of Ames test, reverse mutation assay, chromosomal aberrations assay, and mouse micronucleus assay have shown that salidroside is not genotoxic at a clinical dose (150 mg/60 kg/day) for humans.89,90 Another randomized and controlled trial of 60 breast cancer cases showed that there were no clinical adverse events when an effective dose of salidroside (600 mg/kg/day) was administered during the entire therapeutic process.91 Thus, the lack of adverse effects in the course of pre-clinical and clinical trials indicate that salidroside is promising as a common clinical drug.

Clinical studies
Some publications on clinical efficacy have demonstrated that Rhodiola extracts are helpful for learning and memory, especially concentration, and that they are extremely helpful for patients with mild-to-moderate depression.95–97 Rhodiola extract injection and Rhodiola capsules are widely used for stroke rehabilitation and to treat high-altitude hypoxia clinically. Although many studies have demonstrated clear neuroprotective effects of salidroside in cell lines and/or rat models, none of the salidroside preparations have so far entered medical clinical trials, and there has been no clinical evidence to confirm the efficacy of salidroside. Therefore, highly qualified and large controlled clinical experiments are expected in order to better direct the clinical application of salidroside.

Conclusion
This review article extensively summarized several studies in order to determine the neuropharmacological role of salidroside and its possible underlying mechanisms. According to these studies, salidroside possesses various biological activities in the nervous system, including anti-AD, anti-PD, anti-stroke, cognitive function improvement, mood amelioration, anti-HD, anti-aging, anti-addiction, and anti-epileptic effects. Salidroside has powerful bioactive effects and can regulate oxidative stress, inflammation, apoptosis, the HPA axis, neurotransmission, the cholinergic system, and neural
regeneration. Although the function of salidroside in the central nervous system has been investigated in preclinical tests, no data are available that can provide safe and effective clinical evidence in patients, and definite target protein conjugates for salidroside are still lacking. Therefore, as a bioactive component of traditional Chinese medicine, the applications and efficacy of salidroside in central nervous system diseases require further investigation.

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All authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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The authors report no conflicts of interest in this work.

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