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REVIEW

Targeting glial cells: Unveiling the neuroprotective mechanisms of Ginseng in the brain microenvironment

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Oxidative stress

Abstract The burden imposed by central nervous system disorders (CNSD) on global health is substantial, characterized by a significant impact on quality of life, increased mortality rates, and escalating economic costs. Glial cells, primarily comprising astrocytes, microglia, oligodendrocytes, and oligodendrocyte precursor cells (OPCs, also known as NG2 cells), play crucial and diverse roles in neurological health and disease. In the treatment of CNSD with traditional herbal medicines, ginseng and its active components have made a notable impression. This comprehensive review investigates the interaction between ginseng and these essential glial cells, detailing their contributions to neurological well-being and disease states. Additionally, it thoroughly assesses the effects of ginseng on glial function, highlighting its neuroprotective potential through anti-inflammatory, antioxidative, and other restorative actions *via* complex molecular pathways. Moreover, the review analyzes how ginseng can facilitate neuronal viability and regeneration, as well as modulate signaling cascades, thereby highlighting the therapeutic potential of ginseng in the management of CNSD.

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1. Introduction

Central Nervous System Disorders (CNSD), which include neurodegenerative diseases like Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD), as well as neuropsychiatric disorders like major depressive disorder (MDD), plus incidents of stroke, brain tumors, and multiple sclerosis, impose a substantial global health burden. The taxonomy of CNSD is extensive, with underlying pathogeneses that are multifaceted and complex. The progression of these diseases is often accompanied by cerebral hypoperfusion, neuronal injury, neurological dysregulation, and inflammatory responses, triggering a series of cascading events that may lead to systemic complications. Disorders affecting the nervous system are the leading cause of global disease burden, impacting over 3.4 billion individuals and necessitating urgent development of effective prevention, treatment, and rehabilitation strategies[1]. Epidemiological surveys in recent years have revealed a shift towards a younger demographic affected by CNSD, a trend that correlates strongly with increasing societal pressures and the prevalence of suboptimal health behaviors. Additionally, the distribution of medical resources within a locale is a pivotal determinant of patient prognosis and the life quality post-treatment. Indeed, despite the progressive advancements in global medical technology and diagnostic protocols, the therapeutic armamentarium and technological interventions available for the management of CNSD remain relatively limited. The adverse effects of treatment regimens, pharmacotoxicity, and patient adherence are pivotal elements that critically influence the efficacy of therapeutic interventions.

Glial cells, comprising astrocytes, oligodendrocytes, microglia, and oligodendrocyte precursor cells, are pivotal in the brain microenvironment. Once considered mere supportive cells, glia are now recognized for their dynamic roles in CNSD. They contribute to inflammation, phagocytose debris, promote repair and regeneration, and modulate neurotransmitter metabolism[2]. The dysregulation of glial functions can exacerbate neuronal injury, highlighting their significance as potential targets for therapeutic intervention.

Ginseng (*Panax ginseng* C.A. Mey), a traditional herbal medicine with a long history of use, has garnered attention for its neuroprotective properties. Studies have demonstrated that ginseng and its active substances, such as ginsenosides, exhibit antioxidant and anti-inflammatory effects, which are crucial in mitigating neuronal damage[3]. Furthermore, ginseng has been shown to promote neuronal survival and differentiation, and to improve cognitive function in models of neurodegenerative diseases[4]. Despite these promising findings, the precise mechanisms of ginseng's neuroprotective effects and its clinical applicability remain to be fully elucidated.

We searched for relevant literature using three major biomedical databases: PubMed, Web of Science, and China National Knowledge Infrastructure (CNKI). The search strategy employed the following key terms: ("ginseng" OR "ginseng extract" OR "*Panax ginseng*" OR "ginsenosides" OR "ginseng polysaccharide") AND ("neuroprotection" OR "nervous system disease" OR "nerve injury" OR "neurodegenerative disease" OR "central nervous system disorders" OR "nervous system disorders") and the time range is limited to before July 2025. All controlled studies evaluating the neuroprotection effect and discussing the possible mechanisms of ginseng, ginseng extract, ginsenosides, or other ginseng components were included. The publications of review articles, drug formulations, only *in vitro* studies, no glial evaluation indicators, and non-English were excluded. The PRISMA flowchart for literature screening and inclusion is shown in Fig. 1.

This review aims to explore the interface between glial cells and ginseng's neuroprotective potential within the brain microenvironment. We will synthesize current knowledge on the roles of glial cells in CNSD and the neuroprotective effects of ginseng,

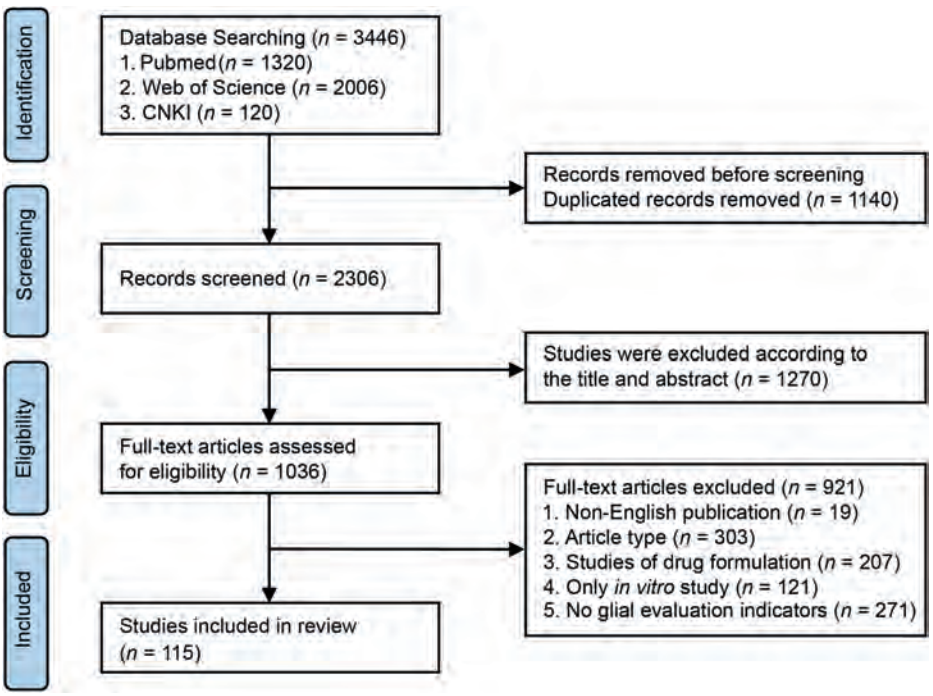


Figure 1 PRISMA flowchart of the literature screening.

with a focus on the molecular and cellular mechanisms involved. By doing so, we intend to highlight the significance of glial cells as therapeutic targets and to provide insights into the development of ginseng-based neuroprotective strategies. The findings may contribute to the advancement of personalized medicine approaches in the treatment of CNSD, ultimately improving the lives of patients and reducing the burden on healthcare systems.

2. Glial cells and their functions in the nervous system

The central nervous system (CNS) is a complex and delicate network whose proper functioning is highly dependent on the diverse roles of glial cells. Among them, the four main types of glial cells, including astrocytes, microglia, oligodendrocytes, and OPCs, play a variety of functions respectively, and interact and coordinate with each other, thereby jointly maintaining a stable microenvironment in the central nervous system (Fig. 2).

2.1. Astrocytes: functions and neuroprotective roles

Astrocytes, characterized by their star-shaped morphology and extensive ramification, are the most abundant glial cells in the CNS. Astrocytes are derived from neural progenitor cells (NPCs) in the subventricular zone (SVZ) and migrate along radial glia processes to populate all areas of the CNS. Mature astrocytes play multiple important roles, such as maintaining the blood−brain barrier (BBB), providing metabolic support to neurons, regulating neurotransmitter levels, and participating in synaptic plasticity[5]. Astrocytes also have a key role in the inflammatory response in the CNS. In a healthy state, they secrete anti-inflammatory cytokines and growth factors, but in response to injury or disease, they can be activated and secrete pro-inflammatory mediators[6].

2.1.1. Maintenance of blood−brain barrier integrity

BBB is a critical interface that protects the brain from potentially harmful substances and pathogens. The transit of molecules and cells across the BBB is finely regulated by a variety of cell types, including astrocytes[7,8]. Astrocytes contribute to BBB functionality by forming specialized structures known as end-feet, which envelop the endothelial cells of brain capillaries[9,10]. Through the expression of tight junction proteins and the regulation of transporters, astrocytes help to maintain the selective permeability of the BBB, thus safeguarding the neural environment. Astrocytes secrete Sonic hedgehog (SHH) and BBB endothelial cells (ECs) express Hedgehog (Hh) receptors, which together promote BBB formation and integrity during embryonic development and adulthood[11,12]. Astrocyte-secreted apolipoprotein E3 (APOE3) suppressed the cyclophilin A (CYPA)−nuclear factor-κB (NF-κB)−matrix-metalloproteinase-9 (MMP9) pathway in pericytes through a lipoprotein receptor, thus counteracting the BBB disruption associated with apolipoprotein E4 (APOE4)[13]. In addition, vascular endothelial growth factor (VEGF) secreted by astrocytes serves as a powerful angiogenic stimulus, facilitating inflammation within the central nervous system through the augmentation of blood−brain barrier permeability and the promotion of immune cell transmigration[14,15]. Consequently, astrocytes modulate the formation, maintenance, and permeability of the BBB, which is commonly disrupted in neurological diseases.

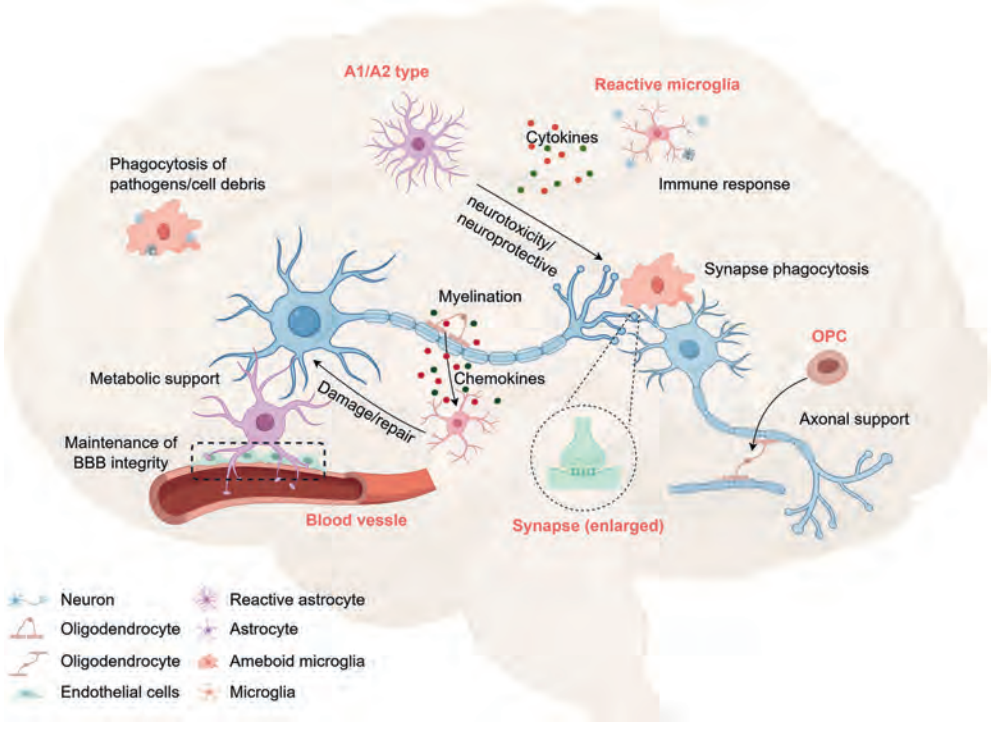


Figure 2 Glial cells and their functions in the nervous system. This diagram shows the intricate roles of three main types of glial cells in the CNS. Neurons are shown in blue, interacting with glial cells. Astrocytes (purple) provide metabolic support to neurons, maintain the integrity of the blood−brain barrier, and participate in neuronal repair processes. Oligodendrocytes are mainly components of neuronal myelin sheath and play an important role in myelin formation and repair. Activated microglial cells are engaging in phagocytosis of pathogens and cell debris, contributing to immune responses through cytokine release, and regulating synapses *via* phagocytosis. The figure emphasizes the crucial and diverse functions of glial cells in maintaining normal neural function and their implications in CNSD. OPC, oligodendrocyte precursor cell. By Figdraw.

2.1.2. *Reactive astrocytes: neuroinflammation or neural repair/regeneration*

Astrocytes play a pivotal role in modulating neuroinflammatory responses. Astrocytes are able to respond to inflammatory signals and promote inflammation. Upon detecting cellular stress or injury, astrocytes undergo a drastic transformation called "reactive astrocytes", in which the expression of many genes is up-regulated so that astrocytes undergo a process of molecular, morphological, and functional remodeling[16], thus participating in the regulation of pathological processes in the body[17]. Reactive astrocytes express multiple receptors, including pattern recognition receptors and cytokine receptors[18]. Thus, astrocytes can promote or limit inflammation by producing immunomodulatory molecules in response to multiple signals in the central nervous system microenvironment[19].

Astrocytes can differentiate into A1 and A2 reactive phenotypes in response to CNS neuroinflammation and ischemia[20]. A1 astrocytes, induced by pro-inflammatory cytokines like interleukin-1α (IL-1α), tumor necrosis factor-alpha (TNF-α), and interferon-γ (IFN-γ), adopt a neurotoxic profile, releasing nitric oxide (NO) and reactive oxygen species (ROS), contributing to synaptic damage and BBB disruption, exacerbating neuroinflammation, and correlating with neuronal loss in diseases such as Alzheimer's and Parkinson's diseases[21,22]. Conversely, A2 astrocytes, triggered by insulin-like growth factor 1 (IGF-1), IL-4, and IL-13, embody a neuroprotective role, secreting neurotrophic factors like glial cell line-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), and neurotrophin-3 (NT-3), supporting neuronal survival and regeneration[23]. The interplay between A1 and A2 phenotypes is pivotal in determining neurological outcomes[24], with therapeutic strategies targeting A2 polarization and suppression of A1 responses being explored for CNS pathologies, highlighting the need to understand the molecular mechanisms governing astrocyte polarization for developing novel treatments.

2.1.3. *Influence on neuronal survival and function*

Astrocytes are essential for neuronal survival and function. Under normal physiological conditions, astrocytes provide metabolic support by shuttling glucose to neurons and removing neurotransmitters from the synaptic cleft[25,26]. Astrocytes also buffer the extracellular environment by regulating ion and water homeostasis[27,28], which is critical for the proper functioning of neurons. Additionally, astrocytes release neurotrophic factors, such as GDNF[29] and BDNF, which can promote neuronal survival and synaptic plasticity[30], thereby contributing to cognitive processes and learning[31]. Following neural injury, astrocytes become activated and contribute to the repair and regeneration processes. Moreover, astrocytes are involved in the formation of the glial scar[32], a barrier that prevents the spread of damage while providing a substrate for axonal regeneration.

In summary, astrocytes are dynamic and multifunctional cells that exert neuroprotective effects through the modulation of neuroinflammation, maintenance of BBB integrity, participation in neural repair, and support of neuronal survival. Elucidating the precise mechanisms underlying these functions is crucial for developing therapeutic strategies aimed at mitigating CNSD.

2.2. *Microglial cells: roles in neuroinflammation and neuroprotection*

Microglial cells, the resident immune cells of the CNS, play a multifaceted role in neuroinflammation and neuroprotection[33]. Continuously monitoring the brain microenvironment, these cells respond to indices of injury, infection, or abnormal cellular dynamics, with their activation and phenotypic plasticity being fundamental to the brain's injury and disease responses[34,35].

2.2.1. *Activation and phenotypic plasticity*

Microglia exhibit a spectrum of activation states, including disease-associated microglia, DAM, and homeostatic phenotypes. Rather than discrete categories, microglial activation represents a dynamic continuum of functional states[36]. Upon encountering stimuli such as pathogens or cell debris, microglia can adopt a predominantly pro-inflammatory state. This state is characterized by the production of cytokines such as TNF-α, interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), which is essential for pathogen elimination and initiating immune responses. However, sustained or excessive pro-inflammatory activation can contribute to neurotoxicity and tissue damage[37,38]. Conversely, microglia can also adopt states associated with resolution of inflammation, tissue repair, and neuroprotection. In these contexts, they release cytokines like interleukin-4 (IL-4), interleukin-10 (IL-10), and interleukin-13 (IL-13), which dampen inflammation and promote wound healing[39]. These repair-associated states are also linked to the phagocytosis of apoptotic cells and the production of neurotrophic factors[40].

Due to the distinct and often opposing roles of these different activation states, a large number of studies have confirmed that modulating microglial responses towards a balanced profile, favoring repair and neuroprotection over chronic pro-inflammation, holds significant therapeutic promise for neurodegenerative diseases[41].

2.2.2. *Neuroinflammation and phagocytosis*

The release of inflammatory mediators by microglia is a critical aspect of their function in the CNS[42]. Microglial cells are a primary source of cytokines in the brain[43]. These cytokines can have both beneficial and detrimental effects, depending on their concentration and the context of their release. For example, while TNF-α can promote neuroinflammation, it also has neuroprotective roles in certain circumstances[44]. Microglia can generate ROS and reactive nitrogen species (RNS), which are part of the innate immune response[45]. However, an imbalance in these oxidative stress products can lead to neuronal damage and exacerbate neurodegenerative processes. Microglia can release neurotoxic substances, including quinolinic acid and NO, which can induce neuronal death[46]. The release of these toxins is often associated with pro-inflammatory activation states and is a key factor in the pathogenesis of various central nervous system disorders[47,48].

Mature microglial cells in the postnatal brain are equipped with a wide range of surface molecules that enable them to respond rapidly to the extracellular environment, including cytokines, chemokines, purines, hormones, and neurotransmitters[49]. Similar to other macrophages resident in tissues, microglia express common markers such as fractalkine receptor C−X3−C motif chemokine receptor 1 (CX3CR1), colony stimulating factor 1 receptor (CSF1R), integrin CD11b, surface glycoprotein F4/80 and CD68, ionized calcium-binding adapter molecule 1 (Iba1), and CD45. However, under steady-state conditions, the expression levels of these markers are generally lower in microglia compared to perivascular macrophages and blood monocytes[50]. Moreover, in the adult brain, microglia exhibit remarkable efficiency in the clearance of dead cells and excessive cellular debris. The

phagocytic activity of microglia is instrumental in determining adult hippocampal neurogenesis[51].

2.2.3. Neuronal damage and repair

Microglial cells are intricately involved in neuronal damage and repair. The neurotoxic effects of microglia can lead to neuronal damage, particularly in the context of chronic neuroinflammation. The release of inflammatory mediators and neurotoxins can result in the degeneration of neuronal processes and cell bodies, contributing to cognitive decline and neurological deficits[33]. Microglia can also influence synaptic health. Through the release of cytokines and the phagocytosis of synaptic components, they can modulate synaptic strength and plasticity[52]. Excessive microglial activity, however, can lead to synaptic stripping and loss, which is observed in neurodegenerative diseases[53,54]. Microglial activation can also affect other glial cells, including astrocytes[55,56]. The interaction between activated microglia and astrocytes can lead to a feedback loop that exacerbates inflammation and impairs neuroprotective functions.

In conclusion, microglial cells are pivotal in the orchestration of neuroinflammatory responses and neuroprotective mechanisms. Their ability to switch between pro-inflammatory and anti-inflammatory phenotypes is a double-edged sword, offering both potential damage and repair in the CNS. Targeting microglial activation and function may represent a promising therapeutic approach for CNSD.

2.3. Oligodendrocytes in myelination and neuroprotection

Oligodendrocytes are a distinct subset of glial cells within the central nervous system that are pivotal for the formation of myelin sheaths enveloping axons. This myelination process is indispensable not only for the facilitation of saltatory conduction of action potentials but also for the provision of metabolic sustenance and the maintenance of axonal viability[57]. Demyelination, a hallmark of pathologies such as multiple sclerosis (MS), can precipitate impaired neural function and underlie a range of neurological deficits.

2.3.1. Myelination

Oligodendrocytes develop a complex network of projections that envelope multiple axons, giving rise to compact myelin sheaths. This elaborate encasement is crucial for facilitating the rapid transmission of action potentials and is regulated by a delicate interplay of transcription factors and signaling pathways[58,59]. In the context of MS, the destruction and attrition of oligodendrocytes result in demyelination and subsequent neurodegeneration. The inflammatory environment characteristic of MS further impairs the functionality of oligodendrocytes and hampers myelin repair, thereby exacerbating disease progression[60]. Ischemic insults in white matter can precipitate oligodendrocyte apoptosis and resultant demyelination, intensifying the injury and impeding recovery. Additionally, dysregulation in myelination and oligodendrocyte physiology has been documented in postmortem brain tissue from schizophrenia patients, suggesting a potential role for these cells in non-inflammatory psychiatric conditions[61].

2.3.2. Axonal support

Oligodendrocytes furnish axons with metabolic support by shuttling lactate and other metabolites, which are critical for the energy metabolism and functional integrity of axons. For instance, the monocarboxylate transporter 1 (MCT1) expressed on oligodendrocytes facilitates the transport of lactate to axons, where it is utilized as an energy substrate, particularly during periods of high neural activity. This metabolic coupling is essential for the maintenance of axonal homeostasis and is compromised in conditions such as MS, where oligodendrocyte dysfunction leads to reduced lactate transport and axonal atrophy[62].

2.3.3. Neuroimmune interactions

Oligodendrocytes engage in dynamic interactions with immune cells, including microglia, and play a pivotal role in modulating the neuroimmune environment[63]. They contribute to the regulation of immune responses and inflammation through the expression of various cytokines and chemokines. For example, oligodendrocytes can secrete interleukin-1 receptor antagonist (IL-1Ra), a natural inhibitor of IL-1β, thereby tempering the pro-inflammatory effects of microglial activation[64]. Furthermore, OPCs have been shown to express chemokines such as CX3CL1, which can interact with the chemokine receptor CX3CR1 on microglia, influencing their activation state and the overall inflammatory tone[65]. Disruption of these interactions, as observed in MS, can lead to an exacerbated inflammatory response and impaired remyelination.

In conclusion, the multifaceted functions of oligodendrocytes underscore their essential role in CNS homeostasis and pathophysiology. The interplay between oligodendrocytes and axons, as well as their neuroimmune interactions, represents a complex and critical axis in the maintenance of neural health and the pathogenesis of neurological diseases.

2.4. OPCs in myelination and synaptic interactions

Oligodendrocyte precursor cells (OPCs, or O-2A cells, also termed NG2 glia) constitute a distinct population of glial cells ubiquitously distributed throughout the central nervous system (CNS). Characterized by the expression of neuron-glial antigen 2 (NG2/CSPG4) and platelet-derived growth factor receptor alpha (PDGFRα), these cells exhibit remarkable proliferative capacity and morphological plasticity, extending highly branched processes that dynamically survey the neural microenvironment[66]. Unlike mature oligodendrocytes, OPCs retain the ability to divide in the adult CNS and serve as the primary source for new oligodendrocytes, playing indispensable roles in developmental myelination, adaptive remyelination, and neural circuit modulation[67].

2.4.1. Myelination and regenerative potential

The canonical function of OPCs is their capacity to differentiate into myelinating oligodendrocytes. During development, OPCs proliferate and migrate extensively before undergoing terminal differentiation, ensheathing axons with myelin[68]. In the adult CNS, they persist in a relatively quiescent state but rapidly proliferate and differentiate in response to demyelinating injuries, such as those occurring in multiple sclerosis or experimental autoimmune encephalomyelitis (EAE)[69]. This regenerative potential is regulated by intricate signaling networks involving growth factors, neurotransmitters, and transcriptional regulators[70]. Single-cell RNA sequencing studies reveal significant heterogeneity within the OPCs population, identifying subsets with enhanced differentiation competence or region-specific adaptations, which critically influence remyelination efficiency[71].

2.4.2. Non-myelinating functions and synaptic interactions

Beyond their role in myelination, OPCs engage in direct synaptic communication with neurons. They form specialized "synaptosomes"—tripartite synaptic structures where OPCs receive

glutamatergic and GABAergic inputs directly from neurons[72]. This neuron−glia signaling modulates OPCs' proliferation, differentiation, and motility, while also influencing neuronal excitability and synaptic plasticity[73]. Furthermore, recent studies reveal that OPCs actively remodel neural circuits through the phagocytic elimination of synapses in an activity-dependent manner, a function independent of oligodendrogenesis. This synaptic engulfment refines circuit connectivity in the developing and adult visual system, positioning OPCs as essential regulators of neural wiring beyond their classical roles[74,75].

2.4.3. Reactive OPCs in pathology

Under pathological conditions (*e.g.*, trauma, ischemia, neurodegeneration), OPCs undergo reactive changes. While their primary response is geared towards oligodendrocyte replacement, reactive OPCs exhibit pleiotropic behaviors. They can secrete pro-inflammatory cytokines and chemokines, amplifying neuroinflammation and influencing microglial activation[76]. Notably, in chronic inflammatory environments like MS lesions or after spinal cord injury, a subset of reactive OPCs may aberrantly differentiate into astrocytes, contributing to glial scar formation and potentially impeding axonal regeneration[77]. Conversely, they also release neuroprotective factors and promote angiogenesis *via* VEGF secretion, supporting tissue repair[78].

3. Impact of ginseng on glial cells

The neuroprotective role of ginseng has been extensively validated. Numerous studies have reported its efficacy and use as an adjunct therapy for a variety of CNSD, including AD, PD, stroke, and depression. Previous studies largely focused on the anti-inflammatory and antioxidant pharmacological mechanisms of ginseng. However, growing evidence suggests that the neuroprotective effects of ginseng in the brain ultimately converge on glial cells directly or indirectly. Consequently, glial cells are likely to be the key players in the therapeutic action of ginseng for neurological conditions.

3.1. Effect of ginseng on astrocytes

3.1.1. Inhibition of astrocyte-mediated inflammation

Ginseng and its bioactive components exhibit significant anti-inflammatory effects in astrocytes through multiple pathways. In $A\beta_{1-40}$-induced AD rat models, ginsenoside Rd suppressed astrocyte activation by reducing GFAP-positive cells and downregulating pro-inflammatory cytokines while upregulating anti-inflammatory IL-10 expression[79]. Similarly, ginsenoside Rb1 ameliorated AD-related neuroinflammation by inhibiting GFAP and IL-1β expression in hippocampal astrocytes[80]. Additionally, the non-saponin polysaccharide fraction (NFP) from Korean Red Ginseng (KRG) significantly attenuated astrocyte activation in the hippocampus and subiculum of 3xTg-AD mice, concurrently reducing Aβ deposition and tau pathology[81].

In depression models, Rb1 suppressed astrocyte-mediated inflammation by downregulating NF-κB-dependent pro-inflammatory cytokines and GFAP expression in LPS-stimulated astrocytes[82]. Rg1 protects against cadmium neurotoxicity primarily by inhibiting astrocyte and microglia activation and subsequent neuroinflammation, consequently alleviating oxidative stress and neuronal damage[83]. Gintonin (GT), a glycolipoprotein fraction isolated from ginseng, reduced hippocampal neuron death and epileptic seizures by attenuating microglial and astrocytic activation, downregulating pro-inflammatory cytokines, and upregulating nuclear factor-erythroid 2 related factor 2 (Nrf2)-mediated antioxidant responses *via* LPAR1/3[84]. Furthermore, GT conferred neuroprotection primarily by modulating immune responses, a critical factor in neuroinflammatory pathogenesis. Ginsenoside Rg3 and Rh2 reduced trimethyltin (TMT)-induced seizures, astrocytic activation, and inflammatory cytokine secretion, while promoting type 2 astrocytic differentiation to protect oligodendrocyte precursor cells[85]. Furthermore, Rh2 mitigated neuropathic pain by suppressing microglial and astrocytic activation and inhibiting pro-inflammatory cytokines like TNF-α, IL-1, and IL-6 through the miRNA-21−TLR8−MAPK pathway[86]. This highlighted Rh2's potential as a therapeutic agent in conditions involving chronic pain and inflammation.

3.1.2. Maintaining astrocyte homeostasis

Ginseng and its bioactive components actively preserve astrocyte integrity and function under pathological conditions. Ginseng total saponins (GTS) reversed corticosterone-induced reductions in hippocampal astrocyte number and structural plasticity[87]. Another study showed that GTS did not significantly change the number of astrocytes after traumatic brain injury but increased the expression of GDNF and the number of GDNF/GFAP co-expressing cells, indicating a protective effect on astrocyte[88]. Korean red ginseng extract (KRGE) enhanced astrocyte proliferation, mitochondrial biogenesis, and neurotrophic secretion *via* HIF-1α[89]. In stroke models, Ginsenoside Rb1 significantly suppressed astrocyte activation in the peri-infarct area, correlating with reduced neurodegeneration and improved neurological function in non-human primates[90]. Ginsenoside Rb1 protected against oxygen-glucose deprivation/reoxygenation (OGD/R)-induced astrocytic injury by improving mitochondrial function and redox homeostasis[91]. This highlighted Rb1's role in astrocyte metabolism and its potential in preventing metabolic stress-induced neurological damage. Similarly, in vascular dementia, *Panax ginseng* extract attenuated cognitive deficits and neuronal injury partly through reducing reactive astrogliosis in the hippocampal CA3 region[92]. Ginsenosides Rd and Rh2 significantly enhanced the cellular viability of astrocytes treated with methylglyoxal, and they also ameliorated the insulin signaling pathway while inhibiting apoptosis, which suggested that Rd, Rh2, and related compounds may hold therapeutic potential in the treatment of neurodegeneration induced by diabetes[93]. Ginsenosides Rg3 and Rh2 contributed to maintaining astrocyte homeostasis by reducing TMT-induced astrocyte death and inhibiting inflammatory cytokine secretion. They functioned through the selective upregulation of the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) pathway and inhibition of extracellular regulated protein kinases (ERK) activation[85]. This signaling pathway modulation is critical for astrocyte survival and function, as it regulates cell death and inflammation. Rg1 prevented astrocyte apoptosis by inhibiting intracellular Ca^{2+} overload, mitochondrial membrane potential loss, and ROS production, thereby reducing neurological deficits *in vivo*[94]. This highlighted Rg1's role in maintaining the cellular integrity of astrocytes, which is essential for their support of neuronal function. Ginsenoside Rf (G-Rf) treatment significantly reversed L-α-aminoadipic acid (L-AAA) induced depression-like behaviors in mice, which was associated with the upregulation of glial fibrillary acidic protein (GFAP) and Ki-67 expression in the prefrontal cortex (PFC) and the attenuation of hippocampal astrocytic alterations, suggesting that G-Rf exerts a protective effect against L-AAA-induced astrocytic ablation in the PFC, thereby mitigating

depressive-like behavioral changes[95]. Ginsenoside Rc effectively reversed astrocyte ablation in the prefrontal cortex of L-AAA-treated mice, significantly increasing GFAP-positive cell density and area while restoring TGF-β expression—a critical astrocyte-derived regulator of microglial homeostasis. Rc further demonstrated anti-apoptotic effects by reducing caspase-3 and elevating Bcl-2 levels, directly countering astrocytic degeneration in this depression model[96]. All these findings underscore the importance of ginseng in astrocyte homeostasis and its potential in treating CNSD.

3.1.3. Protection of the blood−brain barrier

Studies have shown that ginseng and its active components play a vital role in maintaining the BBB function, of which astrocytes are a major component, which has important implications for preventing neurological diseases and protecting brain health. Ginsenoside Rg1 enhanced angiogenesis and functional recovery in spinal cord injury by promoting astrocyte-mediated angiogenesis through the JAK2/STAT3 pathway[97]. This suggested that ginsenoside Rg1 could be a promising candidate for promoting vascular repair and BBB integrity following neurological injury. Compound K (CK), a metabolite of ginseng saponins, ameliorated mild cognitive impairment by repairing intestinal barrier dysfunction, enhancing BBB integrity, and inhibiting astrocyte activation[98]. G-Re reduced spinal inflammation and BBB disruption in experimental autoimmune encephalomyelitis (EAE) multiple sclerosis mice by inhibiting TLR4/MyD88/NF-κB signaling[99]. Furthermore, total saponins of *Panax ginseng* (TSPG) reduced hippocampal neural damage and inflammation, potentially through the suppression of CX3CL1/CX3CR1 signaling, which suggested that TSPG could be effective in treating hippocampal-related disorders by protecting astrocytes and maintaining BBB function[100]. Our latest research showed that ginsenoside Rg2 (G-Rg2) effectively maintained the integrity of the blood−brain barrier in an AD model by inhibiting the TLR4/MyD88/MMP9 inflammatory pathway, which contributed to reduced BBB leakage and enhanced tight junction stability. These findings position G-Rg2 as a promising therapeutic candidate for mitigating BBB dysfunction in AD[101]. Another research showed that KRG improved AD pathology by promoting *Lactobacillus* dominance in the gut microbiota, reducing microglial activation and enhancing blood−brain barrier integrity in mice[102], indicating the significant role of intestinal microbial and the brain−gut axis in neuroprotection. In addition, KRG alleviated depressive symptoms induced by chronic restraint stress (CRS), potentially through increasing astrocyte count and restoring gap junction intercellular communication (GJIC) in the prefrontal cortex[103]. Similarly, Rg1 exhibited antidepressant-like effects by reversing corticosterone-induced GJIC suppression and modulating the expression and phosphorylation of connexin43 (Cx43), the major component of gap junctions in astrocytes[104].

The collective evidence supported the notion that ginseng and its components are valuable in preserving astrocyte function, which is crucial for overall brain health and resilience. The relevant specific studies are shown in Fig. 3 and Table 1[79,80,82,83,94,96,97,99,101,105-116].

3.2. Effect of ginseng on microglial cells

3.2.1. Modulation of activation states

The modulation of microglial activation states by ginseng is a pivotal mechanism in the neuroprotective potential of this traditional herb. Studies have consistently shown that ginsenosides, such as Rg1, Rg3, CK, and Rb1, can effectively regulate microglial activity, which is crucial for maintaining brain health and preventing neurodegenerative diseases.

KRGE could exert neuroprotective effects and diminish behavioral disorder in the MPTP-induced PD model through the inhibition of the activation/infiltration of microglia by inhibiting MAPKs and the NF-κB pathways[117]. A similar study showed that

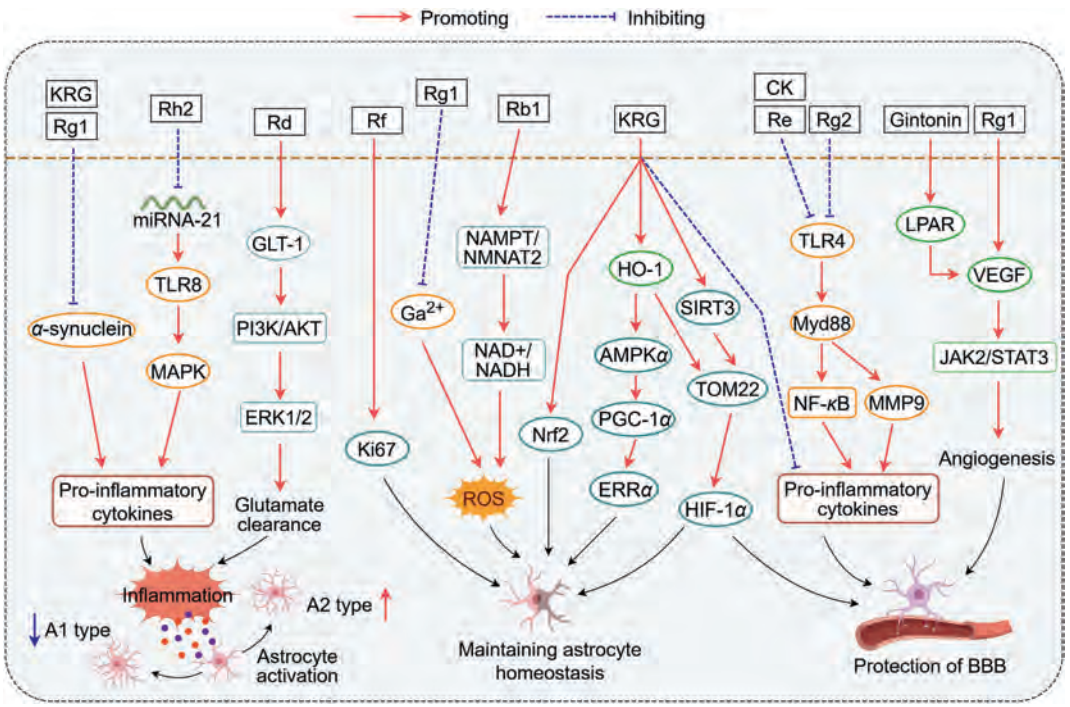


Figure 3 Neuroprotective effects and mechanisms of ginsenosides targeting astrocytes.

Table 1 Neuroprotective effects and mechanisms of ginseng targeting astrocytes.

Ginseng compounds	Cells/animal model	Diseases/model	Mechanism of action	Ref.
Ginsenoside Rd	Sprague−Dawley rats	AD	↓IL-1β, IL-6, TNF-α, S100β; ↑IL-10; ↑HSP70	79
Ginsenoside Rb1	Male Wistar rats	AD	↓IL-1β and Aβ	80
Ginsenoside Rb1	SD rats	Depression	↓NLRP3, p-p65, IL-1β; ↑PINK1 and LC3B; ↑GAP-43, SYN, and PSD-95	82
Ginsenoside Rg1	Male C57BL/6J mice	Cadmium-induced neurotoxicity	↑BDNF-TrkB/Akt; ↑Notch/HES-1 signaling	83
Ginsenoside Rg1	BALB/c mice	Ischemia and reperfusion	↓Intracellular Ca^{2+}, ↓ROS production	94
Ginsenoside Rc	Male C57BI/6 mice	Depression	↓TNF-α, IL-6, and lipocalin-2; ↑TGF-β; ↓caspase-3; ↑Bcl-2	96
Ginsenoside Rg1	SD rats	Spinal cord injury	↑VEGF; ↑JAK2/STAT3 pathway	97
Ginsenoside Re	C57BL/6 mice	Multiple sclerosis	↓TLR4/MyD88/NF-κB	99
Ginsenoside Rg2	Male ICR mice	AD	↓TLR4/MyD88/MMP9; ↑Stability of TJs	101
Ginsenoside Rg1	C57BL/6 mice	PD	↓α-Synuclein-mediated neuroinflammation	105
Ginsenoside Rg1	Male SD rats	Sub-acute aging	↑Neurogenesis; ↑Antioxidant and anti-inflammatory	106
Ginsenoside Rg1	Male Wistar rats	Depression	↓Oxidative damage; ↓IL-1β, IFN-γ, and TNF-α, ↓Bax, caspase 3, and caspase 9	107
Ginsenoside Rg2	3xTg-AD mice	AD	↓TNF-α, IL-1β, and IL-6; ↓ICAM-1 and VCAM-1; ↑p-ERK and *p*-MAPK	108
Ginsenoside Rb1	Male Albino mice	AD	↓Cleaved caspase-3; ↓MDA and AChE; ↑SOD; ↑Synaptophysin	109
Ginsenoside Rb1	Newborn SD rats	Hypoxic-ischemic brain damage (HIBD)	↑SLC7A11, SLC3A2, GPX4, HIF-1α, and GSS; ↓iNOS, IL-18, COX2 and TNF-α	110
Ginsenoside Rb1	C57BL/6 male mice	PD	↑GLT-1; ↓a-synuclein; ↓Glutamate excitotoxicity; ↑Synaptic protein	111
Ginsenoside Rb1	C57BL/6J mice	Ischemic brain injury	↓ROS; ↓NADH dehydrogenase in mitochondrial complex I	112
Ginsenoside Rd	Male SD rats	Stroke	↑PI3K/AKT; ↑ERK1/2 pathways; ↑GLT-1	113
Ginsenoside RK1	APP/PS1 mice	AD	↓p-tau, Bax, and Cleaved caspase 3; ↑Bcl2, p-MAPK, and Nrf2	114
Ginsenoside Rk3	APP/PS1 mice	AD	↑GSH and SOD; ↓MDA, p-Tau; ↑Bcl-2/Bax; ↑AMPK/Nrf2 pathway	115
Ginsenoside Ro	APP/PS1 mice	AD	↑Bcl2; ↓Bax, caspase3, TNF-α, IL-1β, and IL-6; ↓p-p38, p-ERK, and p-JNK	116

gintonin contributed to neuroprotection against MPTP-mediated neurotoxicity and the inflammatory response by inhibition of the MAPKs and NF-κB pathways, thereby inhibiting microglial activation[118]. In a chemobrain mouse model induced by docetaxel, Adriamycin, and cyclophosphamide (DAC), pretreatment with ginsenoside Rg1 prevented cognitive impairment and restored neuronal function by inhibiting M1 polarization and promoting an anti-inflammatory environment[119]. Similarly, in a sub-acute PD model, Rg1 protected dopaminergic neurons by reducing pro-inflammatory cytokines and shifting microglial polarization towards the M2 phenotype, which is associated with neuroprotection and tissue repair[120]. In a chronic mild stress-induced depression model, Rg1's antidepressant effects were attributed to its suppression of inflammasome activation and pro-inflammatory microglial activation, which facilitated hippocampal neurogenesis[121]. Rg1 also demonstrated neuroprotective effects in a cuprizone-induced demyelination model by modulating microglial phenotypes and inhibiting CXCL10-mediated glial response[122].

Panaxytriol, a triterpene sapogenin component of ginseng, demonstrated a pronounced effect on inhibiting microglial activation in LPS-induced brain inflammation, suggesting its role in maintaining a healthy brain microenvironment[123]. CK suppressed the expression of proinflammatory cytokines and inhibited microglial activation *in vitro*, indicating its potential in mitigating neuroinflammation[124]. Additionally, 20(*S*)-protopanaxadiol (PPD) showed neuroprotective effects in a vascular dementia model by inhibiting microglial activation and neuroinflammation[125].

Ginsenoside Rg3 also played a significant role in modulating microglial activation, as it attenuated the up-regulation of pro-inflammatory cytokines and reduced microglial activation in an LPS-induced neuroinflammation model[126]. This finding was echoed in a study where Rg1 protected against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD by regulating the activation of microglia and T cell infiltration in the substantia nigra pars compacta (SNpc) region[127]. In the context of mood disorders, Rg3 ameliorated LPS-induced depression-like behavior by modulating immune activation and microglial activation, highlighting its potential in central nervous system disorders beyond neurodegeneration[128]. Ginsenoside Rb1's neuroprotective effects in a PD model were linked to its ability to suppress microglial overactivation and inhibit the NF-κB pathway, a key mediator of inflammation[129]. Furthermore, GS-KG9, an air-dried and ethanol-extracted white ginseng extract, relieved neuropathic pain by inhibiting microglial activation in specific brain regions, further underscoring the therapeutic potential of ginseng components in neurological conditions[130]. In aged

GPx-1-deficient mice, ginsenoside Re mitigates memory impairments primarily through targeting microglial activation; it reduces microgliosis and disrupts the pathogenic interplay between PAFR and NF-κB specifically within hippocampal microglia[131].

These studies collectively illustrated the diverse and potent effects of ginseng and its components in modulating microglial activation states, which is a critical aspect of neuroprotection and the prevention of CNSD.

3.2.2. Inhibition of inflammation

Ginseng and its bioactive components have been shown to exert significant anti-inflammatory effects on microglial cells, which are pivotal in the neuroprotective potential of ginseng. *Panax ginseng* extract (PGE) exerts antidepressant-like effects on CRS-induced depression by anti-neuroinflammatory and antioxidant (Nrf2/HO-1) activities by inhibiting the hypothalamo−pituitary−adrenal (HPA) axis mechanism[132]. KRG and total saponins effectively inhibited LPS-induced expression of inducible nitric oxide synthase (iNOS), MMP-9, and pro-inflammatory cytokines in microglial cells, as well as suppressed NF-κB and MAPK activities, key upstream signaling molecules in inflammation[133]. Forest-grown ginseng alleviated neuroinflammation and Aβ deposition in AD models by suppressing microglial overexpression and restoring dysregulated amino acid/sphingolipid metabolism[134]. Ginsenoside Rb1 exerted anti-inflammatory effects in various models. In a cerebral ischemia model, Rb1 depressed microglial activation and reduced the expression of TNF-α, IL-6, and cyclooxygenase-2 (COX-2), as well as inhibiting the NF-κB pathway[135]. Systemic administration of Rb1 attenuated Iba1 protein expression and morphological activation of microglia, and significantly reduced the upregulation of *Tnf-α*, *Il-1β*, and *Il*-6 mRNA in the brain tissue following LPS treatment[136]. Additionally, Rb1's neuroprotective effects in a traumatic brain injury model involved attenuation of oxidative stress markers, neuroinflammation, and acetylcholinesterase levels in the cortex and hippocampus[137]. Ginsenoside Rg1, another ginsenoside, ameliorated LPS-induced rotational behavior and loss of tyrosine hydroxylase-positive neurons in the substantia nigra pars compacta, while also inhibiting LPS-induced microglial activation and production of TNF-α, IL-1β, and NO[138]. Furthermore, in a clinically relevant model of sepsis-associated encephalopathy (SAE) induced by cecal ligation and puncture (CLP), Rg1 pretreatment significantly improved survival, attenuated cognitive deficits, and crucially suppressed microglial activation in the hippocampus[139]. Another study showed Rg1 exhibited potent antidepressant effects in a chronic social defeat stress (CSDS) model by suppressing hippocampal microglial activation and reducing pro-inflammatory cytokines, iNOS, and COX-2 expression. This was accompanied by inhibition of JNK/p38 MAPK and NF-κB pathways while enhancing ERK and SIRT1 signaling, collectively attenuating neuroinflammation[140]. Rd, a ginsenoside derivative, inhibited ischemia-induced microglial activation and decreased the expression of various pro-inflammatory cytokines, suppressing NF-κB nuclear translocation and proteasome activity in microglia[141]. Ginsenoside Re inhibited the activation of microglia by promoting the apoptosis of activated microglia and reducing inflammation in a reserpine-induced mouse depression model. Furthermore, the alterations in the BDNF/TrkB/ERK/CREB signaling pathway induced by reserpine in the mouse hippocampus were significantly reversed by Gs-Re[142]. Significantly, Ginsenoside Rk3 has also been demonstrated to suppress the activation of microglia (as evidenced by reduced Iba1 expression) and astrocytes in the hippocampus and cortex of APP/PS1 AD model mice, further supporting the role of ginsenosides in mitigating neuroinflammation[115].

The anti-inflammatory effects of ginsenosides are also mediated through specific pathways. For instance, Rg1's effects against LPS-induced microglia activation were found to involve the G protein-coupled estrogen receptor (GPER), indicating a novel mechanism for its anti-inflammatory action[143]. Ginsenoside Rh2 inhibited the activation of microglia and decreased the release of inflammatory mediators in response to T. *gondii* infection through the TLR4/NF-κB signaling pathway[144]. Ginsenoside Rh3 exerted potent anti-inflammatory effects in LPS-stimulated microglia by inhibiting the expression of iNOS, TNF-α, and IL-6, while promoting hemeoxygenase-1 expression, and modulating NF-κB and Nrf2 activities through the upregulation of silent information regulator factor 2-related enzyme 1 (SIRT1) and the activation of AMPK, which in turn suppresses the PI3K/Akt and JAK1/STAT1 pathways[145]. Furthermore, ginsenoside Rb1's antidepressant effects were linked to its ability to reduce IL-1β and TNF-α expression in hippocampus, serum, and microglia, suggesting a comprehensive anti-inflammatory role[146]. Finally, ginsenoside Re, a ginseng component, inhibited the production of IL-6, TNF-α, NO, and ROS in microglial cells, and suppressed LPS-mediated phosphorylation of CAMK/ERK/JNK/NF-κB signaling, indicating a multifaceted approach to inhibiting neuroinflammation[147]. These findings collectively demonstrated the robust anti-inflammatory properties of ginseng and its components, providing a strong basis for their potential therapeutic use in neurodegenerative diseases characterized by chronic neuroinflammation.

3.2.3. Improvement of phagocytosis

Ginseng and its active components enhance the phagocytic capabilities of microglial cells, which is crucial for the clearance of amyloid-beta (Aβ) aggregates, a hallmark of AD. Ginsenoside Rg3 significantly promoted the uptake, internalization, and digestion of Aβ by microglia. This enhanced phagocytic activity was associated with the up-regulation of MSRA (macrophage scavenger receptor type A), an enzyme involved in the reduction of Aβ-associated oxidative stress[148]. Moreover, Rg1 might induce microglial phagocytosis to reduce Aβ deposits in the hippocampus of AD mice. Rg1 could restore mitophagy and ameliorate memory deficits in the AD mouse through the PINK1−Parkin pathway[149]. Expanding the mechanistic repertoire, recent studies reveal that Rg1 enhances microglial Aβ phagocytosis in aged postoperative cognitive dysfunction (POCD) mice *via* the endo−lysosomal pathway. Specifically, Rg1 upregulates Rab7 (critical for endosomal maturation) and promotes TFEB nuclear translocation. Activated TFEB boosts lysosomal biogenesis and hydrolase activity, thereby accelerating Aβ degradation in an MEK/ERK-dependent manner, offering a novel pathway for Aβ clearance[150]. Furthermore, Rg1-loaded nanovesicles (Rg1@NCM) in ischemic stroke models activated AMPK-dependent pathways, boosting microglial phagocytosis and neutrophil clearance to reduce neuroinflammation[151]. These findings collectively demonstrate that ginsenosides (Rg1 and Rg3) enhance microglial phagocytosis through distinct pathways, highlighting their therapeutic potential for Aβ clearance in diverse CNSD.

In summary, ginseng and its components play multifaceted roles in modulating microglial cells. They regulate activation states, inhibit inflammation, and improve phagocytosis, which provides a strong foundation for potential therapeutic

applications in neurodegenerative diseases (Fig. 4 and Table 2 [119-121,126-129,131,135,136,138-142,146,149-161]).

3.3. *Effect of ginseng on oligodendrocyte lineage cells*

Oligodendrocyte lineage cells are essential for the integrity of the nervous system, primarily through the formation and maintenance of the myelin sheath. Investigations into ginseng and its bioactive components have uncovered their pronounced impact on safeguarding and enhancing the functionality of oligodendrocytes in relation to myelin integrity (Fig. 5 and Table 3[162-167]).

3.3.1. *Protection of myelin from damage*

In MS-related models, ginseng and its bioactive components have demonstrated significant protective effects through dual mechanisms. Some bioactive components from ginseng prevent myelin damage through indirect immunomodulation or anti-inflammatory effects. KRG inhibited cuprizone-induced demyelination by suppressing microglia/macrophage activation, reducing pro-inflammatory mediators (TNF-α, IL-1β, iNOS), and limiting Th1/Th17 cell infiltration[168]. Similarly, in EAE models, G-Re ameliorated demyelination by attenuating BBB disruption and inhibiting the TLR4/MyD88/NF-κB pathway[99]. Furthermore, gintonin reduced immune cell infiltration and regulated Th1/Th17/Treg balance[169]. KRGE has also been shown to suppress spinal cord demyelination by modulating T-cell populations (Th1/Th17 downregulation, Treg upregulation)[162]. Ginsenoside Rd significantly attenuated inflammation and demyelination in EAE mice by reducing BBB permeability, promoting a Th2 cytokine shift (decreasing IFN-γ/increasing IL-4), and restoring neurotrophic factor expression (BDNF/NGF) in the cortex and spinal cord, indicating indirect protection *via* neuroimmune crosstalk[170].

Notably, some bioactive components can directly act on oligodendrocytes, thereby preventing myelin damage. An *in vitro* study showed that gintonin directly stimulates OPC proliferation and differentiation. In primary OPC cultures, gintonin enhances late-stage oligodendrocyte differentiation and protects OPCs from endoplasmic reticulum stress-induced death by modulating unfolded protein responses[163]. This suggested that certain ginseng components can act directly on OPCs to promote myelination, independent of immune modulation. In a chronic PD mouse model, ginsenoside Rg1 directly preserved oligodendrocyte function by maintaining iron-regulated protein homeostasis, improving antioxidant stress responses, and increasing the number of mature oligodendrocytes, thereby shielding the myelin sheath[165].

Collectively, these findings suggested that ginseng and its bioactive components protect myelin from damage through various mechanisms, including anti-inflammatory actions, modulation of immune responses, and direct protection of oligodendrocytes, highlighting their therapeutic potential for myelin disorders.

3.3.2. *Promotion of oligodendrocyte myelination*

Ginseng enhances myelination through direct stimulation of oligodendrocytes and indirect glial crosstalk. Korean Red Ginseng and its ginsenoside Rb1 have been shown to enhance myelination both *in vivo* and *in vitro*. They increased myelin levels and modulate endoplasmic reticulum stress and antioxidant expression in oligodendrocytes, while concurrently reducing leukemia inhibitory factor expression in astrocytes. The non-saponin fraction of KRG promoted the proliferation of OPCs, and the saponin fraction fosters differentiation, both processes mediated by AKT and ERK signaling. Notably, Rb1 significantly increased oligodendrocyte membrane size *in vitro* and myelin formation *in vivo*,

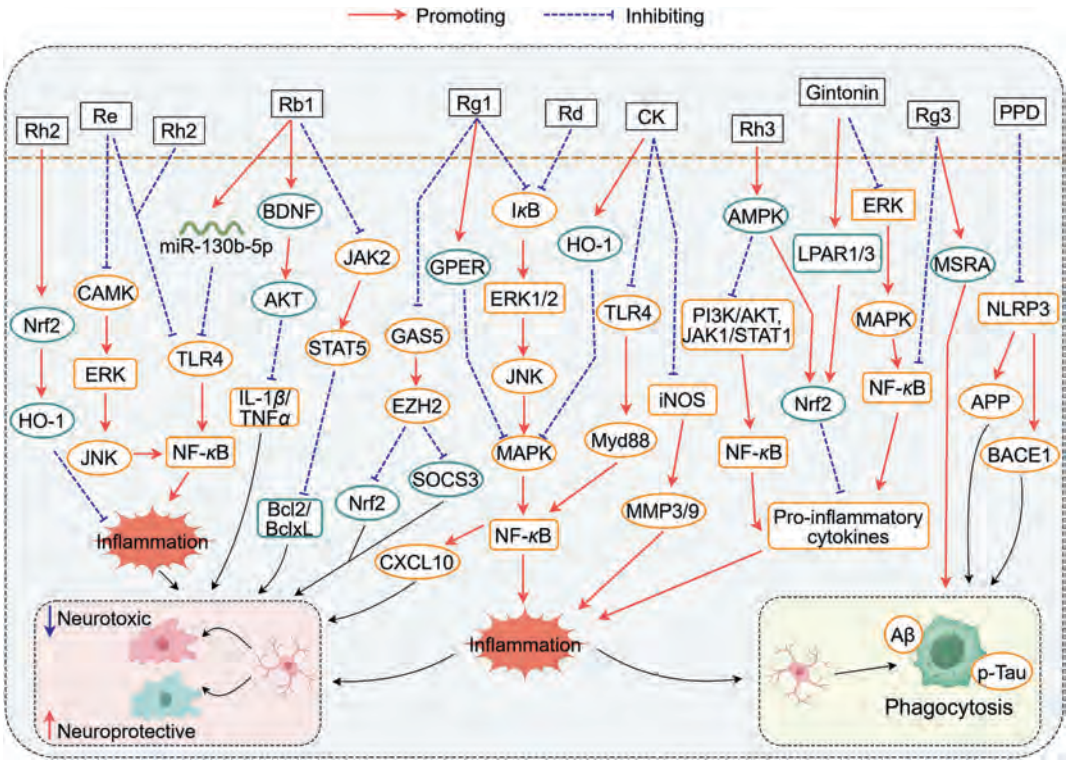


Figure 4 Neuroprotective effects and mechanisms of ginsenosides targeting microglial cells.

Table 2 Neuroprotective effects and mechanisms of ginseng targeting microglial cells.

Ginseng compounds	Cells/animal model	Diseases/model	Mechanism of action	Ref.
Ginsenoside Rg1	C57/BL6J mice	Chemobrain	↓TNF-α and IL-6; ↑IL-4 and IL-10; inhibited microglial M2 to M1 polarization	119
Ginsenoside Rg1	C57BL/6 mice	PD	Shifted the polarization of microglia towards the M2 phenotype from M1; ↓NF-κB nuclear translocation	120
Ginsenoside Rg1	Male C57BL/6J mice	Depression	↓NLRP3; ↑hippocampal neurogenesis	121
Ginsenoside Rg3	C57BL/6 mice	LPS-induced inflammation	↓iNOS and COX-2	126
Ginsenoside Rg1	C57BL/6J mice	PD	↑TH-positive cells; ↓TNF-α, IFN-γ, IL-1β and IL-6	127
Ginsenoside Rg3	ICR mice	Depression	↓NF-κB; restored the systemic balance of tryptophan-kynurenine metabolism	128
Ginsenoside Rb1	Wistar rats	PD	↓Inflammation; ↓NF-κB	129
Ginsenoside Re	C57BL/6 mice; GPx-1 KO mice	Aging-associated memory impairments	↓oxidative insult, PAFR, NF-κB	131
Ginsenoside Rb1	Male SD rats	Cerebral ischemia	↓NF-κB pathway; ↓IL-6	135
Ginsenoside Rb1	C57BL/6 mice	Neuroinflammation	↓IL-1β and IL-6	136
Ginsenoside Rg1	Wistar rats	PD	↓TNF-α, IL-1β and NO; ↓extracellular *p*-IκB, ERK1/2, p38 MAPK	138
Ginsenoside Rg1	Male C57BL/6mice	Sepsis-associated encephalopathy (SAE)	↓TNF-α, IL-1β, and IL-6; ↓LC3-II and p62	139
Ginsenoside Rg1	Male C57BL/6J mice	Depression	↓IL-6, TNF-α and IL-1β; ↓iNOS, COX2, and caspase-9 and -3; ↑MAPK and SIRT1 pathways	140
Ginsenoside Rd	SD rats	Ischemic stroke	↓p-IκBα; ↓NF-κB	141
Ginsenoside Re	Male ICR mice	Depression	↓MDA, IL-1β, IL-6, and TNF-α; ↑BDNF/TrkB/ERK/CREB pathway	142
Ginsenoside Rb1	ICR mice	Depression	↑BDNF; ↑p-AKT/AKT; ↓IL-1β and TNF-α	146
Ginsenoside Rg1	5XFAD mice	AD	↓p-AMPK, *p*-mTOR, and ULK1; ↑LC3B, VPS15, ↑PINK1-Parkin pathway	149
Ginsenoside Rg1	Male C57BL/6 mice	Postoperative cognitive dysfunction (POCD)	↑PSD95, Vglut2, and SYP; ↓MEK/ERK pathway; ↑TFEB nuclear translocation	150
Ginsenoside Rg1	Male C57BL/6J mice	Stroke	↑CD68, *p*-MAPK; ↓Ly6G; ↓cGAS-STING pathway; ↑vascular remodeling	151
Ginsenoside Rb1	Adult male C57BL/6J mice	Depression	↑PPARγ; ↑adult hippocampus neurogenesis	152
Ginsenoside Rb1	Adult male Wistar rats	Spinal cord injury	↑miR-130b-5p; ↓TLR4/NF-κB	153
Ginsenoside Rg1	Male SD rats	Depression	↓GAS5; ↑SOCS3 and NRF2	154
Ginsenoside Rg1	Male SD rats	Cerebral ischemia−reperfusion injury	↓TNF-α, caspase-1 and IL-18 ↓NLRP3, BAX; ↑Pink1, parkin and p62	155
Ginsenoside Rg1	Male C57BL/6 mice	HD	↓Apoptosis; ↓MAPKs and NF-κB pathways	156
Ginsenoside Rd	Sprague−Dawley rats	Focal cerebral ischemia	↓Lipid peroxidation; ↓oxidative damage; ↑CAT, SOD1, SOD2; ↓iNOS and COX-2	157
Ginsenoside Rh2	Female BALB/c mice	Depression	↑5-HT, DA; ↓IDO, IFN-γ, TNF-α and iNOS; ↓HMGB1/TLR4/NF-κB pathway	158
Ginsenoside Rh2	Female BALB/c mice	*T. gondii* infection-induced neuronal injury	↓NLRP3, ASC, cleaved-caspase 1, IL1β	159
Ginsenoside Rk1	Male C57/BL6 mice	PD	↑TH; ↑SIRT3; ↓BAX, Caspase-3	160
Ginsenoside Re	hSOD1^{G93A} mice	Amyotrophic lateral sclerosis	↓loss of motor neurons; ↓p-p38; ↓HO1	161

underscoring their potential for treating myelin-related disorders[166,167]. Gintonin protected against lead-induced cerebellar impairments in developing rats by attenuating glial dysfunction, evidenced by restoring oligodendrocyte populations and myelin basic protein expression, while suppressing neuroinflammation through reduced IL-1β and TNF-α levels. These effects, alongside reduced Purkinje cell damage and apoptosis, contribute to improved motor coordination in offspring[164].

In summary, the findings suggested that ginseng and its components hold considerable promise in the protection of oligodendrocytes and the promotion of myelination through both direct mechanisms and indirect mechanisms, offering promising avenues for the treatment of demyelinating and other CNSD.

4. Molecular mechanisms underlying ginseng−glial cell interaction

Ginseng and its active components exhibit multifaceted molecular mechanisms underlying their interactions with glial cells,

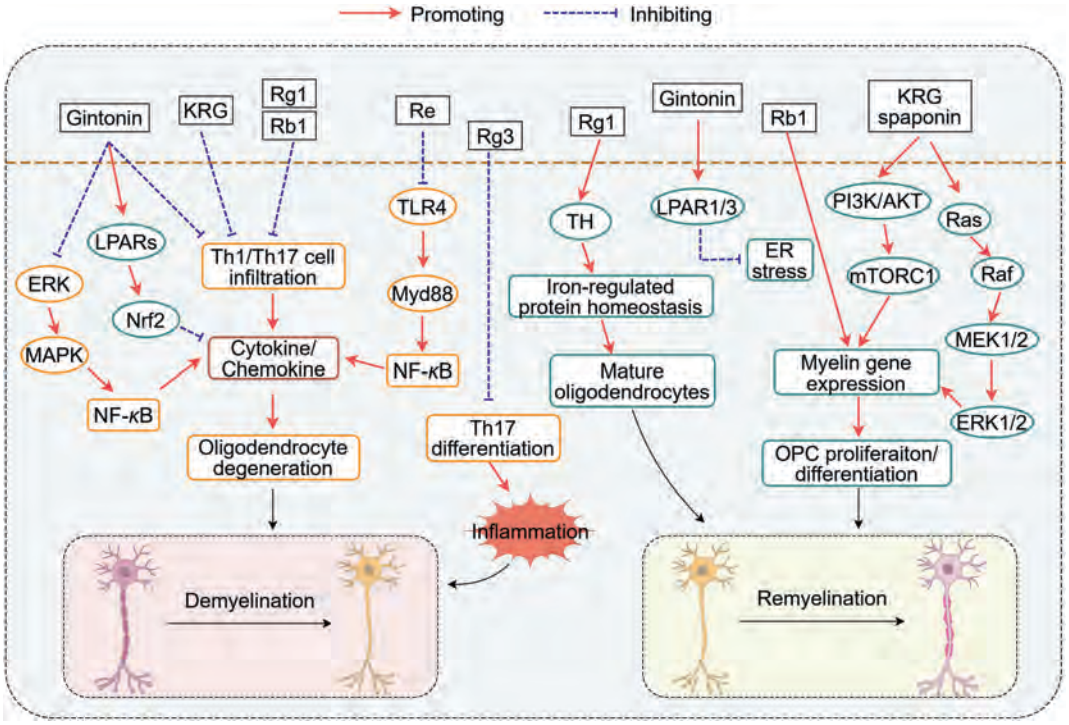


Figure 5 Neuroprotective effects and mechanisms of ginseng targeting oligodendrocytes.

Table 3 Neuroprotective effects and mechanisms of ginseng targeting oligodendrocytes.

Ginseng compounds	Cells/animal models	Diseases/model	Mechanism of action	Ref.
KRGE	Female Lewis rat	Multiple sclerosis	↓Th1 and Th17 T cells; ↑regulatory T cells; ↓IFN-γ, IL-17, and IL-23	162
Gintonin	Primary OPC cultures	Myelin diseases	↓endoplasmic reticulum stress; modulating unfolded protein responses	163
Gintonin	Sprague−Dawley rats	Brain maldevelopment	↑BDNF, Sirt1, MBP, GAD67, LPAR1 and Bcl2; ↓Bax, IL1β and TNF-α;	164
Ginsenoside Rg1	Male C57BL/6 mice	PD	↑tyrosine hydroxylase and anti-oxidant stress; maintained the iron-regulated protein homeostasis by ferritin	165
Ginsenoside Rb1	C57BL/6N female mice	Demyelination	↑expression of myelin genes, ER stress markers, and antioxidants.	166
Ginsenoside Rb1	C57BL/6N male mice	Myelin-related disorder	↑AKT and ERK signaling	167

conferring neuroprotective effects against oxidative stress and inflammation, which are pivotal in various CNSD.

4.1. Anti-oxidative stress (via mitochondria)

Ginseng and its bioactive components exhibit anti-oxidative stress properties, which are critical for protecting glial cells from oxidative stress-caused damage. The mitochondria, the powerhouse of the cells, are particularly susceptible to oxidative stress, and ginseng has been shown to exert its neuroprotective effects through mitochondrial-mediated pathways.

In the G93A-SOD1 transgenic mouse model of amyotrophic lateral sclerosis (ALS), gintonin was found to extend mouse survival and alleviate motor dysfunctions. This effect was associated with the attenuation of oxidative stress, as evidenced by decreased expression of NAD(P) quinone oxidoreductase 1 and reduced oxidative stress-related ferritin, Iba1-immunoreactive microglia, S100β-immunoreactive astrocytes, and Olig2-immunoreactive oligodendrocytes[171]. Ginsenosides Rg3 and Rh2, as major rare ginsenosides, have been demonstrated to serve as neuroprotective agents in a TMT-intoxicated mouse model. These ginsenosides mitigated oxidative stress by improving antioxidant enzyme activity, reducing neuronal loss, and inhibiting astrocyte activation in the mouse brain. The protective mechanisms of Rg3 and Rh2 involved the selective upregulation of the PI3K/Akt pathway and inhibition of ERK activation, promoting type 2 astrocyte differentiation to protect oligodendrocyte precursor cells from TMT toxicity without further inflammatory activation[85].

KRGE enhanced mitochondrial function in astrocytes by inducing the expression of HIF-1α and VEGF. KRGE-induced SIRT3 activation in normoxic astrocytes increases oxygen consumption and mitochondrial membrane potential through the Tom22−HIF-1α pathway, which is independent of estrogen-related receptor α (ERRα) and involves PHD2-mediated HIF-1α stability[172]. Furthermore, KRGE increased the number of astrocytes in mouse brain samples and stimulated astrocyte

proliferation *in vitro*, enhancing mitochondrial biogenesis as evidenced by increased Mitotracker staining, ATP production, and O_2 consumption rates. This was accompanied by elevated expression of proteins associated with mitochondrial electron transport, which is dependent on HIF-1α[89]. KRGE also enhanced mitochondrial function in astrocytes, which is crucial for neurovascular function repair post-TBI, by upregulating heme oxygenase-1 (HO-1) and the HO-1−Tom20 axis, leading to increased oxygen consumption and ATP production[173,174]. Ginsenoside-Rg1 ameliorates stress-induced depression-like behaviors in rats primarily by suppressing glial cell activation (microglia and astrocytes) and oxidative stress, thereby reducing neuronal apoptosis and synaptic deficits in the hippocampal CA1 region[107].

In summary, ginseng and its bioactive components, such as gintonin, ginsenosides Rg3 and Rh2, and KRGE, exert their neuroprotective effects through mitochondrial-mediated pathways, reducing oxidative stress and enhancing mitochondrial function. These findings underscore the importance of ginseng in the treatment and prevention of neurodegenerative diseases associated with oxidative stress.

4.2. *Anti-inflammatory*

Ginseng's anti-inflammatory properties are a pivotal aspect of its neuroprotective effects on glial cells. Various studies have demonstrated the ability of ginseng and its bioactive components to modulate inflammatory responses in the brain.

Red ginseng extract (RGE) significantly attenuated Aβ-induced mitochondrial dysfunction and reduced Aβ deposition in 5XFAD mice, concurrently suppressing microglial and astrocytic activation, thereby ameliorating neuroinflammation and neurodegeneration[175].

Gintonin significantly attenuated striatal toxicity in Huntington's disease models by suppressing microglial activation and reducing the expression of key pro-inflammatory mediators (*e.g.*, IL-1β, IL-6, TNF-α, COX-2, iNOS) in the striatum, primarily through activation of the LPA receptor−Nrf2 signaling pathway[176].

In a PD model, oral administration of ginsenoside Rg1 significantly mitigated the mortality, behavioral deficits, and dopamine neuron loss induced by MPTP. The neuroprotective effects of Rg1 were linked to its anti-neuroinflammatory properties, as evidenced by the reduction of reactive astrocytes and microglia, and the decreased release of cytokines such as TNF-α and IL-1β in the SNpc[105].

Total saponin extract (TSE) derived from red ginseng (a steamed and dried ginseng product), along with ginsenosides Rb1 and its metabolite CK, exerted antinociceptive effects against peripheral and central neuropathic pain. These compounds alleviated ectopic pain and hyperalgesia, and suppressed the activation of spinal microglia/macrophages and astrocytes, as well as the expression of inflammatory mediators such as IL-1β, IL-6, iNOS, and Cox-2[177].

GS-E3D (pectin lyase-modified red ginseng extracts) and GS-KG9 have been shown to inhibit BBB disruption following hippocampal neuronal death in streptozotocin-induced diabetic rats. These extracts reduced BBB permeability, suppressed matrix metalloproteinase-9 expression, inhibited macrophage infiltration, and decreased the activation of hippocampal microglia and astrocytes, along with the mRNA expression of proinflammatory cytokines such as *Tnf-*α, *Il-1*β, *Il-6*, and mediators including *Cox-2* and *inos*[178]. In an $AlCl_3$-induced AD model, ginsenoside Rb1 notably suppressed microglial activation and astrogliosis, which contributed to attenuated neuroinflammation, reduced neuronal apoptosis and synaptic loss, and mitigated accumulation of amyloid-β and phosphorylated tau protein[109].

Pretreatment with KRGE before immunization with myelin basic protein peptide conferred protective effects against spinal cord demyelination by inhibiting the recruitment and activation of immune cells, including microglia, and by modulating the expression of inflammatory mediators. This effect was associated with the downregulation of p38 MAPK and NF-κB signaling pathways in microglia/macrophages, T cells, and astrocytes[179].

Water-soluble ginseng oligosaccharides (WGOS) protected against scopolamine-induced learning and memory deficits and downregulated the hyperexpression of proinflammatory cytokines *Il-1*β and *Il*-6 mRNA and astrocyte activation in the hippocampus[180].

The ethanolic extract of black ginseng (BGE), enriched with unique and rare ginsenosides resulting from the specialized heating process of *Panax ginseng* roots, demonstrated potent anti-neuroinflammatory properties by inhibiting the overproduction of pro-inflammatory mediators in LPS-stimulated BV2 microglial cells. This effect was attributed to the suppression of NF-κB, p38 MAPK, and JNK signaling pathways, and was mediated through the negative regulation of the TLR4/MyD88 pathway. Ginsenosides Rd and Rg3 within BGE were identified as key inhibitors of inflammatory mediator production[181]. In addition, ginsenoside Rd significantly ameliorates ischemic brain injury by attenuating early oxidative damage and suppressing sequential inflammatory responses, notably inhibiting microglial activation and reducing pro-inflammatory mediators derived from activated glial cells[157]. Similarly, ginsenoside Ro exhibited significant anti-inflammatory effects in an APP/PS1 AD model. It reduced neuroinflammation by suppressing both IBA1-positive microglia and GFAP-positive astrocytes in the cerebral cortex, concurrently decreasing pro-inflammatory cytokines. Crucially, Ro inhibited the MAPK pathway by significantly reducing phosphorylation levels of p38 and JNK, suggesting this pathway as a key mechanism for its modulation of glial-mediated inflammation[116]. Complementing these findings, ginsenoside RK1 demonstrated potent suppression of microglial and astrocyte activation in the hippocampus and cortex of APP/PS1 mice. Its anti-inflammatory effects were mediated through activation of the AMPK/Nrf2 signaling pathway, which not only reduced glial-mediated neuroinflammation but also ameliorated oxidative stress, with efficacy surpassing the standard AD drug donepezil[114].

Ginsenoside Rh2 protects against *Toxoplasma gondii*-induced neuronal injury by directly binding to NLRP3 in microglia, thereby inhibiting the NLRP3 inflammasome signaling pathway and suppressing neuroinflammation, while also reducing parasite proliferation *via* interaction with TgCDPK1[159].

Moreover, the neuroprotective role of ginseng was intertwined with the activation of the Nrf2 pathway, which is crucial for preventing oxidative stress and neuroinflammation. For instance, ginseng pretreatment improved acute sensorimotor deficits and long-term functional recovery following pdMCAO predominantly through Nrf2 activation, which was linked to the attenuation of reactive astrogliosis[182]. Similarly, the attenuation of reactive gliosis and improved neurological outcomes post-ischemic injury were associated with ginseng or DMF-mediated Nrf2 activation[183]. Nrf2 mediates the neuroprotective effect of KRG in a permanent cerebral ischemia model by suppressing gliosis[184].

Collectively, these studies underscored the anti-inflammatory potential of ginseng and its bioactive components, which may be

harnessed for the treatment of neurodegenerative diseases characterized by neuroinflammation.

4.3. Promoting neuron survival or regeneration

Ginseng and its bioactive components, such as ginsenosides Rg1, Rb1, and the Rb fraction, exhibit a multifaceted neuroprotective potential by promoting neuron survival and regeneration. These compounds target various pathways to mitigate neuronal damage and support cognitive function.

Ginsenoside Re rescues methamphetamine-induced dopaminergic degeneration by inhibiting PKCδ, thereby attenuating pro-inflammatory microglial activation and mitochondrial oxidative stress in the striatum[185]. Rg1 has been shown to protect hippocampal integrity by enhancing NSCs/NPCs survival, reducing astrocyte activation, and increasing cell proliferation. This protection was accompanied by an anti-oxidative and anti-inflammatory effect, which collectively improved cognitive abilities and neurogenesis in aged rats[106]. Similarly, Rb1 and the Rb fraction from ginseng demonstrated neuroprotective effects against excitotoxicity and ischemic injury, respectively, by preserving neuronal integrity and inhibiting apoptosis[112,186].

The neuroprotective effects of ginseng are not limited to direct neuronal protection but also extend to the modulation of glial cell function. For instance, treatments with ginseng and dimethyl fumarate reduced hippocampal neuronal degeneration following hypoxia−ischemia, in part by attenuating reactive gliosis and maintaining astrocytic functions[187]. KRG prevented dopaminergic neuronal death and behavioral deficits, which may be mediated, at least in part, through the modulation of gut microbiota composition, specifically suppressing pro-inflammatory and elevating anti-inflammatory bacteria[188].

Additionally, SGB121, an enhanced ginsenoside formulation, protected against high-fat diet-induced brain damage by inhibiting oxidative stress and cellular senescence, and by promoting mitochondrial autophagy[189]. Red ginseng extract (RGE) improved functional recovery after spinal cord injury by reducing microglial aggregation and inflammation, and by upregulating neuroprotective factors[190].

Ginsenoside Rb1 also showed promise in mitigating depressive-like behaviors by promoting a pro-neurogenic phenotype in microglia and enhancing neural precursor cell proliferation and differentiation, which contributed to improved hippocampal neurogenesis[152].

In summary, ginseng and its bioactive components promote neuron survival and regeneration through a combination of direct neuronal protection and glial cell modulation. These effects are mediated through anti-oxidative, anti-inflammatory, and pro-neurogenic mechanisms, making ginseng a promising candidate for the treatment of various CNSD. This is exemplified by the neuroprotective effects observed in herbal decoctions like KaiXin San[191,192], Yinao Fujian formula[193], and Kyung-Ok-Ko[194], which demonstrate the capacity to ameliorate depressive symptoms, inflammation, and cognitive impairments.

4.4. Regulation of signaling pathways

Ginseng and its bioactive components modulate various signaling pathways in glial cells to exert neuroprotective effects. Ginsenoside Rd, as a major component in ginseng, upregulates the expression of the astrocytic glutamate transporter-1 (GLT-1) through the PI3K/AKT and ERK1/2 pathways, enhancing glutamate clearance and preventing excitotoxicity following brain ischemia[113]. Similarly, ginsenoside Rb1 promotes GLT-1 expression in astrocytes *via* NF-κB nuclear translocation, reducing glutamate excitotoxicity and ameliorating motor deficits in a Parkinson's disease model[111]. Additionally, ginsenoside Rg1 promotes Cx43 expression in astrocytes, reversing corticosterone-induced changes and modulating degradation pathways, which may ameliorate depressive symptoms by enhancing gap junctions[195]. Another research showed ginsenoside Rg1 ameliorated cerebral ischemia−reperfusion injury by enhancing Pink1/Parkin-mediated mitophagy in microglia, thereby suppressing NLRP3 inflammasome activation and subsequent neuroinflammation[155]. In a Huntington's disease model, ginsenoside Rg1 ameliorated neuronal loss and inflammation by suppressing the MAPKs and NF-κB signaling pathways[156]. Additionally, Rg1 mitigated depression-like behaviors by suppressing lncRNA growth arresting-specific 5 (GAS5), leading to the activation of NRF2 and suppressor of cytokine signaling 3 (SOCS3) and improved mitochondrial function, which was associated with reduced microglial activation[154].

Gintonin induced autophagy in astrocytes *via* an mammalian target of rapamycin (mTOR)-mediated pathway, which was enhanced by the LPA receptor and involves the upregulation of autophagic markers[196]. Gintonin also stimulated astrocytic glycogenolysis, ATP production, and glutamate uptake under hypoxic conditions, providing a protective mechanism through LPA receptor-regulated Ca^{2+} transients[197]. Furthermore, gintonin mediated the release and expression of VEGF in astrocytes, which may contribute to neuroprotection under hypoxic conditions[198].

KRGE modulated the expression of plasminogen activator inhibitor-1 (PAI-1) in astrocytes through the activation of PI3K, p38, ERK1/2, and JNK, which may play a role in regulating tPA (tissue plasminogen activator) activity and neuroprotection in ischemic conditions[199]. Ginsenoside Re exhibited neuroprotective effects against neuroinflammation in an ALS model by inhibiting the TLR4 pathway and reducing the expression of pro-inflammatory proteins and phospho-p38[161].

Panaxytriol inhibited the LPS-induced activation of microglia and the subsequent production of NO and proinflammatory cytokines by suppressing NF-κB nuclear translocation, without affecting the Nrf2−ARE and MAPK pathways[200]. Ginsenoside Rb1 protected against spinal cord injury by upregulating miR-130b-5p, which targeted TLR4, thereby inhibiting the NF-κB pathway and reducing neuronal apoptosis and inflammation[153].

Ginsenoside Rk1 exerts neuroprotective effects in Parkinson's disease models by significantly suppressing microglial activation and neuroinflammation in the substantia nigra and striatum, while activating SIRT3-mediated Nrf2/HO-1 signaling to mitigate oxidative stress and neuronal apoptosis. These mechanisms collectively ameliorate motor deficits and dopaminergic neuron loss[160]. Ginsenoside CK alleviates brain aging by inhibiting ferroptosis *via* modulation of the ASK1−MKK7−JNK signaling pathway, leading to enhanced Nrf2 nuclear accumulation. Crucially, CK significantly attenuates the activation of both microglia and astrocytes, reducing neuroinflammation and oxidative stress, thereby improving cognitive function and neuronal integrity in aging models[201].

Ginsenoside Rh2 ameliorates depression-like behaviors in offspring of *Toxoplasma gondii*-infected mothers by inhibiting microglial activation and neuroinflammation *via* suppression of the HMGB1/TLR4/NF-κB signaling pathway in the prefrontal cortex[158]. Ginsenoside Rb1 ameliorates hypoxic-ischemic brain

damage in neonatal rats by inhibiting ferroptosis and glial activation. This neuroprotective effect is achieved through restoring System Xc activity and antioxidant capacity, while suppressing lipid peroxidation and inflammation[110].

Ginsenoside Rg2 alleviates neurovascular damage in AD by suppressing astrocyte activation, reducing neuroinflammation and Aβ/tau pathology, while restoring neuronal/vascular markers *via* MAPK−ERK pathway activation[108].

These findings collectively demonstrated that ginseng and its active components regulate key signaling pathways in glial cells, which is a critical aspect of their neuroprotective potential.

4.5. Structure−function relationships of ginsenosides targeting glial cells

The extensive studies reviewed herein provide compelling evidence for the neuroprotective efficacy of ginseng and its bioactive components, particularly ginsenosides, across diverse CNSD. However, despite the wealth of data describing these biological activities, establishing definitive, causal links between the specific structural features of individual ginsenosides and their distinct functional outcomes on different glial cell types remains a significant challenge. While direct, systematic mapping of ginsenoside structural variations to specific glial functional outcomes remains challenging, emerging pharmacological evidence supports plausible structure-function relationships. Nevertheless, emerging data and pharmacological principles allow us to hypothesize plausible structure−function relationships governing ginsenoside interactions with glial cells. Key structural elements likely influencing their activity include: core sapogenin type, glycosylation patterns, stereochemistry, and lipophilicity.

Ginsenosides are classified based on their sapogenin backbone: protopanaxadiol (PPD)-type and protopanaxatriol (PPT)-type (Table 4). These core structures possess distinct three-dimensional conformations and polarity, potentially leading to differential binding affinities for receptors or enzymes on specific glial cells. For instance, PPT-type Rg1 frequently demonstrates potent effects on astrocytic functions, while PPD-type Rb1 and CK often show strong anti-inflammatory effects in microglia and modulation of oligodendrocyte differentiation/myelination.

Highly glycosylated ginsenosides like Rb1 generally exhibit lower bioavailability and potentially reduced ability to cross the BBB compared to their less glycosylated or deglycosylated metabolites (*e.g.*, CK, Rh2, and Rg3). Deglycosylation often enhances membrane permeability and access to intracellular targets within glia. CK, a major intestinal metabolite of Rb1/Rd lacking sugars at C-20, demonstrates superior potency in suppressing microglial NF-κB activation compared to its parent compounds[124].

The location of sugar attachments (C-3, C-6, C-20 for PPD; C-6, C-20 for PPT) significantly alters molecular shape and interaction surfaces. For example, the tetra-glycoside structure of Rg1 (PPT-type, sugars at C-6 and C-20) appears critical for activating astrocytic BDNF/TrkB signaling and SIRT1-mediated mitochondrial pathways[94]. Removal of specific sugars (*e.g.*, generating metabolites like F1 from Rg1) can shift activity towards other functions, such as enhancing microglial phagocytosis. While glucose is predominant, variations exist. The specific sugar type might influence solubility, stability, and receptor recognition.

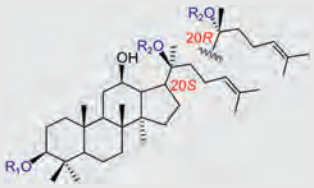
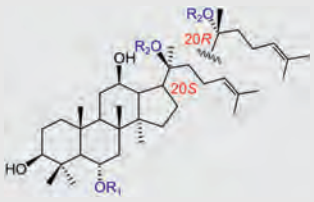
Another important feature of ginsenosides is that they have different stereoscopic configurations. The stereochemical configuration at key positions, notably C-20 (20*S vs.* 20*R*), may impact their biological activity. In addition, structural features directly influence lipophilicity, affecting passive diffusion across cell membranes (including glial cells) and distribution within the CNS. Less polar derivatives like CK, Rh2, and Rg3 generally show better cellular penetration than highly glycosylated precursors.

5. The prospects of ginseng in treating CNSD

5.1. Clinical trials of ginseng in CNSD

Current clinical evidence regarding the beneficial effects of ginseng in treating CNSD remains limited but promising. For AD, a cross-sectional study of 160 non-demented older adults (aged

Table 4 Structure−function relationships of ginsenosides targeting glial cells.

Compd. structure	Ginsenoside	R_1	R_2	Formula	Glial cell target
	Protopanaxadiol	-H	-H	$C_{30}H_{52}O_3$	Microglia
	Compound K	-H	-Glc	$C_{36}H_{62}O_8$	Microglia; Astrocyte
	Ginsenoside-Rb1	-Glc(2 → 1)Glc	-Glc(6 → 1)Glc	$C_{42}H_{72}O_{13}$	Microglia; Astrocyte; Oligodendrocyte
	Ginsenoside-Rc	-Glc(2 → 1)Glc	-Glc(6 → 1)Araf	$C_{53}H_{90}O_{22}$	Microglia; Astrocyte
	Ginsenoside-Rd	-Glc(2 → 1)Glc	-Glc	$C_{48}H_{82}O_{18}$	Microglia; Astrocyte
	Ginsenoside-Rg3	-Glc(2 → 1)Glc	-H	$C_{42}H_{72}O_{13}$	Microglia; Astrocyte
PPD-type	Ginsenoside-Rh2	-Glc	-H	$C_{36}H_{62}O_8$	Microglia; Astrocyte
	Protopanaxatriol	-H	-H	$C_{30}H_{52}O_4$	Microglia; Astrocyte
	Ginsenoside-Re	-Glc(2 → 1)Rha	-Glc	$C_{48}H_{82}O_{18}$	Microglia; Astrocyte
	Ginsenoside-Rf	-Glc(2 → 1)Glc	-H	$C_{42}H_{72}O_{14}$	Astrocyte
	Ginsenoside-Rg1	-Glc	-Glc	$C_{42}H_{72}O_{14}$	Microglia; Astrocyte; Oligodendrocyte
	Ginsenoside-Rg2	-Glc(2 → 1)Rha	-H	$C_{42}H_{72}O_{13}$	Astrocyte
	Ginsenoside-Rh1	-Glc	-H	$C_{36}H_{62}O_9$	Microglia
PPT-type					

65−90) demonstrated that ginseng intake (primarily red ginseng) significantly improved delayed episodic memory, the earliest AD-specific cognitive marker, but not non-memory cognition. Notably, this benefit was moderated by APOE4 status: ginseng's positive effect was pronounced in APOE4-negative individuals but absent in APOE4 carriers. Optimal cognitive benefits were associated with long-term intake (≥5 years) initiated in midlife (<65 years)[202]. These findings align with a 24-week randomized open-label trial where Korean Red Ginseng (KRG; 4.5 or 9.0 g/day) significantly improved Alzheimer's Disease Assessment Scale (ADAS) and Korean version of the Mini Mental Status Examination (K-MMSE) scores in 61 AD patients, indicating KRG's safety and feasibility for long-term AD management[203].

For ischemic stroke, a phase II trial (NCT00591084) of 199 patients showed Ginsenoside Rd enhanced 15-day National Institutes of Health Stroke Scale (NIHSS) scores and may be of some benefit in the management of acute ischemic stroke[204]. Besides, an extended work (NCT00815763) also showed that ginsenoside Rd improved the primary outcome of acute ischemic stroke and had an acceptable adverse-event profile[205].

For depression, an additional 6-week prospective open-label trial in 36 patients with difficult-to-treat major depressive disorder (MDD) showed that KRG augmentation (RGA; 2 g/day) significantly improved outcomes. The remission rate was 39.3% (MADRS≤10) and 57.1% (CGI-I≤2), with a 44.4% reduction in MADRS scores from baseline. Adverse events were generally mild (headache: 25%), supporting RGA's tolerability and potential efficacy in treatment-resistant MDD[206], though larger randomized trials are needed for confirmation.

5.2. *Safety and limitations*

Although generally well-tolerated in clinical studies focusing on CNSD, a comprehensive evaluation of ginseng, particularly KRG and isolated ginsenosides, necessitates careful consideration of its safety profile and the inherent limitations of the existing evidence base. Clinical trials consistently report mild and transient adverse events (AEs) associated with ginseng, primarily gastrointestinal disturbances (*e.g.*, nausea, diarrhea, abdominal discomfort), dermatological reactions (pruritus, rash), headaches, and dizziness, though these occur at rates comparable to placebo groups. For instance, a 24-week multicenter study of 1000 healthy adults administered 2 g/day KRG found no significant differences in AE incidence or adverse drug reactions, with discontinuation rates due to AEs similarly low (1.2% *vs.* 1.4%)[207]. Likewise, studies on specialized ginseng derivatives like the gintonin-enriched fraction (GEF) and fermented red ginseng (FRG) observed minimal AEs, predominantly mild diarrhea or dyspepsia, none deemed definitively treatment-related[208,209]. Notably, serious AEs (SAEs) were rare and unrelated to intervention, while laboratory parameters (liver/kidney function, hematology) and vital signs remained stable across trials. A double-blind, randomized, placebo-controlled trial (RCT) also showed that the daily intake of 2 g of KRG for 24 weeks was found to be safe and well-tolerated in healthy adults, with no significant difference in adverse events or adverse drug reactions compared to placebo[207].

Overall, ginseng and its active substances demonstrate a favorable safety profile in clinical studies, with no clearly reported significant adverse reactions, providing assurance for their broader clinical application.

6. Conclusions and future directions

In conclusion, this review highlights the pivotal role of glial cells as therapeutic targets for ginseng's neuroprotective effects in CNS disorders. Ginseng and its bioactive components modulate glial function through multifaceted mechanisms—suppressing neuroinflammation, reducing oxidative stress, enhancing phagocytosis, promoting remyelination, and maintaining blood−brain barrier integrity. These actions collectively support neuronal survival and functional recovery in models of neurodegeneration (AD, PD, and ALS), stroke, mental disorders, and demyelinating diseases like MS.

Despite the robust preclinical evidence and promising early clinical findings, significant gaps and challenges remain, necessitating focused future research. Specifically, efforts should be directed towards: 1) Deepening mechanistic understanding, particularly for understudied glia. Researches have disproportionately focused on astrocytes and microglia. Priority must be given to elucidating oligodendrocyte and OPCs-specific mechanisms. This includes a detailed investigation into how ginseng promotes remyelination efficiency, provides metabolic support to axons, and protects oligodendrocytes from stress-induced death. Ginseng's protective effects on oligodendrocytes and myelin involve dual pathways: direct OPC targeting (*e.g.*, gintonin-induced proliferation; Rb1-driven AKT/ERK-mediated differentiation) and indirect immunomodulation (*e.g.*, KRGE suppression of neuroinflammation). Future studies should employ OPC-specific conditional knockouts and spatial transcriptomics to resolve the spatiotemporal contributions of these mechanisms. The intriguing role of OPCs in synaptic remodeling *via* phagocytosis and their phenotypic plasticity in pathology represents a critical, largely unexplored frontier. Utilizing advanced techniques like single-cell/nuclei RNA sequencing (scRNA-seq/snRNA-seq) and spatial transcriptomics will be indispensable for dissecting the heterogeneity within oligodendrocyte lineage cells, identifying specific responsive subtypes, and mapping ginseng-induced transcriptional and functional changes *in situ*. 2) Advancing Clinical Translation and Validation. Moving beyond small-scale or open-label studies, large-scale RCTs with longer durations are imperative to definitively establish ginseng's efficacy, optimal dosing, and long-term safety profile across different CNSD. 3) Exploring gut−brain axis interactions. Emerging evidence suggests ginseng modulates gut microbiota and gut barrier function, which can subsequently influence systemic metabolism and neuroinflammation. Future research must dissect this gut−brain axis communication, identifying key microbial metabolites influenced by ginseng and determining how these signals modulate glial cell activation states and BBB function. 4) Overcoming delivery challenges. The relatively large size and polarity of key ginsenosides and polysaccharides limit their BBB penetration and brain bioavailability. Innovative drug delivery strategies are essential, which include: developing nanoparticle formulations or utilizing exosome-based delivery systems to enhance brain uptake; exploring structural modifications of ginsenosides to improve BBB permeability while retaining or enhancing bioactivity, and investigating intranasal delivery routes as a potential bypass of the BBB.

By integrating the wisdom of traditional Chinese medicine with contemporary scientific inquiry, we may uncover novel therapeutic strategies that harness the neuroprotective properties of ginseng and other herbal extracts, offering hope for patients with CNSD. The role of glial cells as a crucial interface in these processes cannot be overstated, and further research in this area is essential for advancing our understanding and treatment of brain diseases.

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Author contributions

Yajun Wang: conceptualization; methodology; writing-original draft. Ming Zhang: supervision; writing-review & editing. Wei Li: review & editing; funding acquisition. All authors have read and agree to be accountable for all aspects of work ensuring integrity and accuracy, and publication of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. GNSD Collaborators. Global, regional, and national burden of disorders affecting the nervous system, 1990-2021: a systematic analysis for the global Burden of Disease Study 2021. *Lancet Neurol* 2024;**23**:344−81.
2. Garden GA, Campbell BM. Glial biomarkers in human central nervous system disease. *Glia* 2016;**64**:1755−71.
3. Lu J, Wang X, Wu AX, Cao Y, Dai XL, Liang YD, et al. Ginsenosides in central nervous system diseases: pharmacological actions, mechanisms, and therapeutics. *Phytother Res* 2022;**36**:1523−44.
4. Zheng MM, Xin YZ, Li YJ, Xu FX, Xi XZ, Guo H, et al. Ginsenosides: a potential neuroprotective agent. *BioMed Res Int* 2018; **2018**:8174345.
5. Lee H-G, Wheeler MA, Quintana FJ. Function and therapeutic value of astrocytes in neurological diseases. *Nat Rev Drug Discov* 2022;**21**: 339−58.
6. Giovannoni F, Quintana FJ. The role of astrocytes in CNS inflammation. *Trends Immunol* 2020;**41**:805−19.
7. Sofroniew MV. Astrocyte barriers to neurotoxic inflammation. *Nat Rev Neurosci* 2015;**16**:249−63.
8. Engelhardt B, Coisne C. Fluids and barriers of the CNS establish immune privilege by confining immune surveillance to a two-walled castle moat surrounding the CNS castle. *Fluids Barriers CNS* 2011;**8**:4.
9. Zhao Z, Nelson AR, Betsholtz C, Zlokovic BV. Establishment and dysfunction of the blood−brain barrier. *Cell* 2015;**163**:1064−78.
10. Xu L, Nirwane A, Yao Y. Basement membrane and blood−brain barrier. *Stroke Vasc Neurol* 2019;**4**:78−82.
11. Alvarez JI, Dodelet-Devillers A, Kebir H, Ifergan I, Fabre PJ, Terouz S, et al. The Hedgehog pathway promotes blood−brain barrier integrity and CNS immune quiescence. *Science* 2011;**334**:1727−31.
12. Alvarez JI, Katayama T, Prat A. Glial influence on the blood brain barrier. *Glia* 2013;**61**:1939−58.
13. Bell RD, Winkler EA, Singh I, Sagare AP, Deane R, Wu Z, et al. Apolipoprotein E controls cerebrovascular integrity *via* cyclophilin A. *Nature* 2012;**485**:512−6.
14. Argaw AT, Asp L, Zhang J, Navrazhina K, Pham T, Mariani JN, et al. Astrocyte-derived VEGF-A drives blood−brain barrier disruption in CNS inflammatory disease. *J Clin Investig* 2012;**122**:2454−68.
15. Argaw AT, Gurfein BT, Zhang Y, Zameer A, John GR. VEGF-mediated disruption of endothelial CLN-5 promotes blood−brain barrier breakdown. *Proc Natl Acad Sci U S A* 2009;**106**:1977−82.
16. Escartin C, Galea E, Lakatos A, O'callaghan JP, Petzold GC, Serrano-Pozo A, et al. Reactive astrocyte nomenclature, definitions, and future directions. *Nat Neurosci* 2021;**24**:312−25.
17. Linnerbauer M, Wheeler MA, Quintana FJ. Astrocyte crosstalk in CNS inflammation. *Neuron* 2020;**108**:608−22.
18. Colombo E, Farina C. Astrocytes: key regulators of neuroinflammation. *Trends Immunol* 2016;**37**:608−20.
19. Farina C, Aloisi F, Meinl E. Astrocytes are active players in cerebral innate immunity. *Trends Immunol* 2007;**28**:138−45.
20. Lawrence JM, Schardien K, Wigdahl B, Nonnemacher MR. Roles of neuropathology-associated reactive astrocytes: a systematic review. *Acta Neuropathol Commun* 2023;**11**:42.
21. Liddelow SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L, et al. Neurotoxic reactive astrocytes are induced by activated microglia. *Nature* 2017;**541**:481−7.
22. Yun SP, Kam TI, Panicker N, Kim S, Oh Y, Park JS, et al. Block of A1 astrocyte conversion by microglia is neuroprotective in models of Parkinson's disease. *Nat Med* 2018;**24**:931−8.
23. Yang QQ, Zhou JW. Neuroinflammation in the central nervous system: symphony of glial cells. *Glia* 2018;**67**:1017−35.
24. Fan YY, Huo J. A1/A2 astrocytes in central nervous system injuries and diseases: angels or devils?. *Neurochem Int* 2021;**148**:105080.
25. Bélanger M, Allaman I, Magistretti PJ. Brain energy metabolism: focus on astrocyte-neuron metabolic cooperation. *Cell Metab* 2011; **14**:724−8.
26. Bonvento G, Bolaños JP. Astrocyte-neuron metabolic cooperation shapes brain activity. *Cell Metab* 2021;**33**:1546−64.
27. Tong X, Ao Y, Faas GC, Nwaobi SE, Xu J, Haustein MD, et al. Astrocyte Kir4.1 ion channel deficits contribute to neuronal dysfunction in Huntington's disease model mice. *Nat Neurosci* 2014;**17**:694−703.
28. Rasmussen MK, Mestre H, Nedergaard M. Fluid transport in the brain. *Physiol Rev* 2022;**102**:1025−151.
29. Duarte Azevedo M, Sander S, Tenenbaum L. GDNF, a neuron-derived factor upregulated in glial cells during disease. *J Clin Med* 2020;**9**:456.
30. Liu YY, Huo D, Zeng LT, Fan GQ, Shen T, Zhang TM, et al. Mesencephalic astrocyte-derived neurotrophic factor (MANF): structure, functions and therapeutic potential. *Ageing Res Rev* 2022;**82**:101763.
31. Sun WF, Liu ZH, Jiang X, Chen MB, Dong H, Liu J, et al. Spatial transcriptomics reveal neuron−astrocyte synergy in long-term memory. *Nature* 2024;**627**:374−81.
32. Sofroniew MV, Vinters HV. Astrocytes: biology and pathology. *Acta Neuropathol* 2010;**119**:7−35.
33. Arcuri C, Mecca C, Bianchi R, Giambanco I, Donato R. The pathophysiological role of microglia in dynamic surveillance, phagocytosis and structural remodeling of the developing CNS. *Front Mol Neurosci* 2017;**10**:191.
34. Provenzano F, Pérez MJ, Deleidi M. Redefining microglial identity in health and disease at single-cell resolution. *Trends Mol Med* 2021;**27**: 47−59.
35. Cserép C, Pósfai B, Lénárt N, Fekete R, László ZI, Lele Z, et al. Microglia monitor and protect neuronal function through specialized somatic purinergic junctions. *Science* 2020;**367**:528−37.
36. Savage JC, Carrier M, Tremblay M. Morphology of microglia across contexts of health and disease. *Methods Mol Biol* 2019;**2034**:13−26.
37. Colonna M, Butovsky O. Microglia function in the central nervous system during health and neurodegeneration. *Annu Rev Immunol* 2017;**35**:441−68.
38. Guo S, Wang H, Yin Y. Microglia polarization from M1 to M2 in neurodegenerative diseases. *Front Aging Neurosci* 2022;**14**:815347.
39. Tang Y, Le WD. Differential roles of M1 and M2 microglia in neurodegenerative diseases. *Mol Neurobiol* 2016;**53**:1181−94.
40. Orihuela R, Mcpherson CA, Harry GJ. Microglial M1/M2 polarization and metabolic states. *Br J Pharmacol* 2016;**173**:649−65.
41. Sun JF, Chen F, She LY, Zeng YQ, Tang H, Ye BZ, et al. YOD1 regulates microglial homeostasis by deubiquitinating MYH9 to promote the pathogenesis of Alzheimer's disease. *Acta Pharm Sin B* 2025;**15**:331−48.
42. Ferro A, Auguste YSS, Cheadle L. Microglia, cytokines, and neural activity: unexpected interactions in brain development and function. *Front Immunol* 2021;**12**:703527.

43. Kettenmann H, Hanisch UK, Noda M, Verkhratsky A. Physiology of microglia. *Physiol Rev* 2011;**91**:461−553.
44. Kraft AD, Mcpherson CA, Harry GJ. Heterogeneity of microglia and TNF signaling as determinants for neuronal death or survival. *Neurotoxicology* 2009;**30**:785−93.
45. Simpson DSA, Oliver PL. ROS generation in microglia: understanding oxidative stress and inflammation in neurodegenerative disease. *Antioxidants* 2020;**9**:743.
46. Harry GJ. Microglia during development and aging. *Pharmacol Ther* 2013;**139**:313−26.
47. Hickman S, Izzy S, Sen P, Morsett L, El Khoury J. Microglia in neurodegeneration. *Nat Neurosci* 2018;**21**:1359−69.
48. Gao C, Jiang JW, Tan YY, Chen SD. Microglia in neurodegenerative diseases: mechanism and potential therapeutic targets. *Signal Transduct Targeted Ther* 2023;**8**:359.
49. Tay TL, Savage JC, Hui CW, Bisht K, Tremblay M. Microglia across the lifespan: from origin to function in brain development, plasticity and cognition. *J Physiol* 2017;**595**:1929−45.
50. Greter M, Merad M. Regulation of microglia development and homeostasis. *Glia* 2013;**61**:121−7.
51. Hanisch UK, Kettenmann H. Microglia: active sensor and versatile effector cells in the normal and pathologic brain. *Nat Neurosci* 2007; **10**:1387−94.
52. Chen ZH, Jalabi W, Hu WW, Park HJ, Gale JT, Kidd GJ, et al. Microglial displacement of inhibitory synapses provides neuroprotection in the adult brain. *Nat Commun* 2014;**5**:4486.
53. Kang YJ, Hyeon SJ, Mcquade A, Lim J, Baek SH, Diep YN, et al. Neurotoxic microglial activation *via* IFNγ-induced Nrf2 reduction exacerbating Alzheimer'S disease. *Adv Sci (Weinh)* 2024;**11**: e2304357.
54. Isik S, Yeman Kiyak B, Akbayir R, Seyhali R, Arpaci T. Microglia mediated neuroinflammation in Parkinson's disease. *Cells* 2023;**12**: 1012.
55. Jha MK, Jo M, Kim JH, Suk K. Microglia-astrocyte crosstalk: an intimate molecular conversation. *Neuroscientist* 2019;**25**:227−40.
56. Domingues HS, Portugal CC, Socodato R, Relvas JB. Oligodendrocyte, astrocyte, and microglia crosstalk in myelin development, damage, and repair. *Front Cell Dev Biol* 2016;**4**:71.
57. Clayton BLL, Tesar PJ. Oligodendrocyte progenitor cell fate and function in development and disease. *Curr Opin Cell Biol* 2021;**73**: 35−40.
58. Li JX, Fiore F, Monk KR, Agarwal A. Spatiotemporal calcium dynamics orchestrate oligodendrocyte development and myelination. *Trends Neurosci* 2025;**48**:377−88.
59. Buchanan J, Da Costa NM, Cheadle L. Emerging roles of oligodendrocyte precursor cells in neural circuit development and remodeling. *Trends Neurosci* 2023;**46**:628−39.
60. Falcão AM, Van Bruggen D, Marques S, Meijer M, Jäkel S, Agirre E, et al. Disease-specific oligodendrocyte lineage cells arise in multiple sclerosis. *Nat Med* 2018;**24**:1837−44.
61. Fessel J. Abnormal oligodendrocyte function in schizophrenia explains the long latent interval in some patients. *Transl Psychiatry* 2022;**12**:120.
62. Philips T, Mironova YA, Jouroukhin Y, Chew J, Vidensky S, Farah MH, et al. MCT1 deletion in oligodendrocyte lineage cells causes late-onset hypomyelination and axonal degeneration. *Cell Rep* 2021;**34**:108610.
63. Niu J, Tsai HH, Hoi KK, Huang N, Yu G, Kim K, et al. Aberrant oligodendroglial−vascular interactions disrupt the blood−brain barrier, triggering CNS inflammation. *Nat Neurosci* 2019;**22**:709−18.
64. Zhou YT, Zhang J, Wang L, Chen Y, Wan YS, He Y, et al. Interleukin-1β impedes oligodendrocyte progenitor cell recruitment and white matter repair following chronic cerebral hypoperfusion. *Brain Behav Immun* 2017;**60**:93−105.
65. Wu XM, Liu Y, Qian ZM, Luo QQ, Ke Y. CX3CL1/CX3CR1 axis plays a key role in ischemia-induced oligodendrocyte injury *via* p38MAPK signaling pathway. *Mol Neurobiol* 2016;**53**:4010−8.
66. Dimou L, Gallo V. NG2-glia and their functions in the central nervous system. *Glia* 2015;**63**:1429−51.
67. Hill RA, Nishiyama A. NG2 cells (polydendrocytes): listeners to the neural network with diverse properties. *Glia* 2014;**62**:1195−210.
68. Nishiyama A, Suzuki R, Zhu X. NG2 cells (polydendrocytes) in brain physiology and repair. *Front Neurosci* 2014;**8**:133.
69. Zawadzka M, Rivers LE, Fancy SP, Zhao C, Tripathi R, Jamen F, et al. CNS-resident glial progenitor/stem cells produce Schwann cells as well as oligodendrocytes during repair of CNS demyelination. *Cell Stem Cell* 2010;**6**:578−90.
70. Marques S, Zeisel A, Codeluppi S, Van Bruggen D, Mendanha Falcão A, Xiao L, et al. Oligodendrocyte heterogeneity in the mouse juvenile and adult central nervous system. *Science* 2016;**352**: 1326−9.
71. Marques S, Van Bruggen D, Vanichkina DP, Floriddia EM, Munguba H, Väremo L, et al. Transcriptional convergence of oligodendrocyte lineage progenitors during development. *Dev Cell* 2018;**46**:504−17.
72. Bergles DE, Roberts JD, Somogyi P, Jahr CE. Glutamatergic synapses on oligodendrocyte precursor cells in the hippocampus. *Nature* 2000;**405**:187−91.
73. Sakry D, Neitz A, Singh J, Frischknecht R, Marongiu D, Binamé F, et al. Oligodendrocyte precursor cells modulate the neuronal network by activity-dependent ectodomain cleavage of glial NG2. *PLoS Biol* 2014;**12**:e1001993.
74. Xiao Y, Petrucco L, Hoodless LJ, Portugues R, Czopka T. Oligodendrocyte precursor cells sculpt the visual system by regulating axonal remodeling. *Nat Neurosci* 2022;**25**:280−4.
75. Auguste YSS, Ferro A, Kahng JA, Xavier AM, Dixon JR, Vrudhula U, et al. Oligodendrocyte precursor cells engulf synapses during circuit remodeling in mice. *Nat Neurosci* 2022;**25**:1273−8.
76. Pandey S, Shen K, Lee SH, Shen YA, Wang Y, Otero-García M, et al. Disease-associated oligodendrocyte responses across neurodegenerative diseases. *Cell Rep* 2022;**40**:111189.
77. Bradbury EJ, Burnside ER. Moving beyond the glial scar for spinal cord repair. *Nat Commun* 2019;**10**:3879.
78. Yuen TJ, Silbereis JC, Griveau A, Chang SM, Daneman R, Fancy SPJ, et al. Oligodendrocyte-encoded HIF function couples postnatal myelination and white matter angiogenesis. *Cell* 2014;**158**: 383−96.
79. Liu JF, Yan XD, Li L, Zhu Y, Qin KF, Zhou LF, et al. Ginsennoside Rd attenuates cognitive dysfunction in a rat model of Alzheimer's disease. *Neurochem Res* 2012;**37**:2738−47.
80. Lin JW, Gao SY, Wang TQ, Shen Y, Yang WY, Li Y, et al. Ginsenoside Rb1 improves learning and memory ability through its anti-inflammatory effect in Aβ1-40 induced Alzheimer's disease of rats. *Am J Transl Res* 2019;**11**:2955−68.
81. Kim S, Shin SJ, Nam Y, Park YH, Kim BH, Park HH, et al. Korean red ginseng polysaccharide as a potential therapeutic agent targeting tau pathology in Alzheimer's disease. *Int J Biol Macromol* 2024;**263**: 130516.
82. Li YN, Li JN, Yang LX, Ren FF, Dong KQ, Zhao ZH, et al. Ginsenoside Rb1 protects hippocampal neurons in depressed rats based on mitophagy-regulated astrocytic pyroptosis. *Phytomedicine* 2023; **121**:155083.
83. Ren TT, Yang JY, Wang J, Fan SR, Lan R, Qin XY. Gisenoside Rg1 attenuates cadmium-induced neurotoxicity *in vitro* and *in vivo* by attenuating oxidative stress and inflammation. *Inflamm Res* 2021;**70**: 1151−64.
84. Choi JH, Kwon TW, Jo HS, Ha Y, Cho IH. Gintonin, a Panax ginseng-derived LPA receptor ligand, attenuates kainic acid-induced seizures and neuronal cell death in the hippocampus *via* anti-inflammatory and anti-oxidant activities. *J Ginseng Res* 2023;**47**: 390−9.
85. Hou JG, Xue JJ, Wang Z, Li W. Ginsenoside Rg3 and Rh2 protect trimethyltin-induced neurotoxicity *via* prevention on neuronal apoptosis and neuroinflammation. *Phytother Res* 2018;**32**:2531−40.

86. Fu YY, Cen JK, Song HL, Song SY, Zhang ZJ, Lu HJ. Ginsenoside Rh2 ameliorates neuropathic pain by inhibition of the miRNA21-TLR8-mitogen-activated protein kinase axis. *Mol Pain* 2022;**18**: 17448069221126078.
87. Chen L, Wang X, Lin ZX, Dai JG, Huang YF, Zhao YN. Preventive effects of ginseng total saponins on chronic corticosterone-induced impairment in astrocyte structural plasticity and hippocampal atrophy. *Phytother Res* 2017;**31**:1341−8.
88. Hu BY, Liu XJ, Qiang R, Jiang ZL, Xu LH, Wang GH, et al. Treatment with ginseng total saponins improves the neurorestoration of rat after traumatic brain injury. *J Ethnopharmacol* 2014;**155**: 1243−55.
89. Park J, Lee M, Kim M, Moon S, Kim S, Kim S, et al. Prophylactic role of Korean red ginseng in astrocytic mitochondrial biogenesis through HIF-1α. *J Ginseng Res* 2022;**46**:408−17.
90. Yoshikawa T, Akiyoshi Y, Susumu T, Tokado H, Fukuzaki K, Nagata R, et al. Ginsenoside Rb1 reduces neurodegeneration in the peri-infarct area of a thromboembolic stroke model in non-human primates. *J Pharmacol Sci* 2008;**107**:32−40.
91. Liu Y, Wang X, Xie J, Tang MK. Regulation of NAD(+)/NADH redox involves the protective effects of ginsenoside Rb1 against oxygen-glucose deprivation/reoxygenation-induced astrocyte lesions. *Int J Mol Sci* 2023;**24**:16059.
92. Zhu JD, Wang JJ, Zhang XH, Yu Y, Kang ZS. Panax ginseng extract attenuates neuronal injury and cognitive deficits in rats with vascular dementia induced by chronic cerebral hypoperfusion. *Neural Regen Res* 2018;**13**:664−72.
93. Chu JM, Lee DK, Wong DP, Wong RN, Yung KK, Cheng CH, et al. Ginsenosides attenuate methylglyoxal-induced impairment of insulin signaling and subsequent apoptosis in primary astrocytes. *Neuropharmacology* 2014;**85**:215−23.
94. Sun CH, Lai XQ, Huang XY, Zeng YY. Protective effects of ginsenoside Rg1 on astrocytes and cerebral ischemic−reperfusion mice. *Biol Pharm Bull* 2014;**37**:1891−8.
95. Kim Y, Lee HY, Choi YJ, Cho SH. Antidepressant effects of ginsenoside Rf on behavioral change in the glial degeneration model of depression by reversing glial loss. *J Ginseng Res* 2020;**44**:603−10.
96. Kwon D, Kim Y, Cho S-H. Antidepressant effects of ginsenoside Rc on L-alpha-aminoadipic acid-induced astrocytic ablation and neuroinflammation in mice. *Int J Mol Sci* 2024;**25**:9673.
97. Yin SY, Xia FY, Zou WJ, Jiang FX, Shen KL, Sun BH, et al. Ginsenoside Rg1 regulates astrocytes to promote angiogenesis in spinal cord injury via the JAK2/STAT3 signaling pathway. *J Ethnopharmacol* 2024;**334**:118531.
98. Yan XJ, Bai X, Fu RZ, Duan ZG, Zeng W, Zhu CH. Ginsenoside compound K alleviates D-galactose-induced mild cognitive impairment by modulating gut microbiota-mediated short-chain fatty acid metabolism. *Food Funct* 2024;**15**:9037−52.
99. Oh J, Kwon TW, Choi JH, Kim Y, Moon SK, Nah SY, et al. Ginsenoside-Re inhibits experimental autoimmune encephalomyelitis as a mouse model of multiple sclerosis by downregulating TLR4/MyD88/NF-κB signaling pathways. *Phytomedicine* 2024;**122**: 155065.
100. Qin M, Chen C, Wang N, Yu D, Yu SM, Wang XY, et al. Total saponins of panax ginseng *via* the CX3CL1/CX3CR1 axis attenuates neuroinflammation and exerted antidepressant-like effects in chronic unpredictable mild stress in rats. *Phytother Res* 2023;**37**:1823−38.
101. Lu YW, Wang YJ, Wang Z, Ren S, Gong XJ, Hu JN, et al. Ginsenoside Rg2 alleviates astrocyte inflammation and ameliorates the permeability of the Alzheimer's disease related blood−brain barrier. *Phytomedicine* 2024;**135**:156063.
102. Lee M, Lee SH, Kim MS, Ahn KS, Kim M. Effect of Lactobacillus dominance modified by Korean red ginseng on the improvement of Alzheimer's disease in mice. *J Ginseng Res* 2022;**46**:464−72.
103. Zheng QL, Zhu HY, Xu X, Chu SF, Cui LY, Dong YX, et al. Korean red ginseng alleviate depressive disorder by improving astrocyte gap junction function. *J Ethnopharmacol* 2021;**281**:114466.
104. Xia CY, Chu SF, Zhang S, Gao Y, Ren Q, Lou YX, et al. Ginsenoside Rg1 alleviates corticosterone-induced dysfunction of gap junctions in astrocytes. *J Ethnopharmacol* 2017;**208**:207−13.
105. Heng Y, Zhang QS, Mu Z, Hu JF, Yuan YH, Chen NH. Ginsenoside Rg1 attenuates motor impairment and neuroinflammation in the MPTP-probenecid-induced parkinsonism mouse model by targeting α-synuclein abnormalities in the substantia nigra. *Toxicol Lett* 2016; **243**:7−21.
106. Zhu JH, Mu XY, Zeng J, Xu CY, Liu J, Zhang MS, et al. Ginsenoside Rg1 prevents cognitive impairment and hippocampus senescence in a rat model of D-galactose-induced aging. *PLoS One* 2014;**9**:e101291.
107. Li Y, Wang LY, Wang P, Fan CQ, Zhang P, Shen J, et al. Ginsenoside-Rg1 rescues stress-induced depression-like behaviors *via* suppression of oxidative stress and neural inflammation in rats. *Oxid Med Cell Longev* 2020;**2020**:2325391.
108. Ye XJ, Shao S, Wang YB, Su WW. Ginsenoside Rg2 alleviates neurovascular damage in 3xTg-AD mice with Alzheimer's disease through the MAPK-ERK pathway. *J Chem Neuroanat* 2023;**133**: 102346.
109. Shalaby AM, Alnasser SM, Ahmed Khairy D, Alabiad MA, Alorini M, Jaber FA, et al. The neuroprotective effect of ginsenoside Rb1 on the cerebral cortex changes induced by aluminium chloride in a mouse model of Alzheimer's disease: a histological, immunohistochemical, and biochemical study. *J Chem Neuroanat* 2023;**129**: 102248.
110. Zhang M, Lin W, Tao XY, Zhou W, Liu ZM, Zhang Z, et al. Ginsenoside Rb1 inhibits ferroptosis to ameliorate hypoxic-ischemic brain damage in neonatal rats. *Int Immunopharmacol* 2023;**121**: 110503.
111. Zhang YL, Liu Y, Kang XP, Dou CY, Zhuo RG, Huang SQ, et al. Ginsenoside Rb1 confers neuroprotection *via* promotion of glutamate transporters in a mouse model of Parkinson's disease. *Neuropharmacology* 2018;**131**:223−37.
112. Ni XC, Wang HF, Cai YY, Yang D, Alolga RN, Liu B, et al. Ginsenoside Rb1 inhibits astrocyte activation and promotes transfer of astrocytic mitochondria to neurons against ischemic stroke. *Redox Biol* 2022;**54**:102363.
113. Zhang X, Shi M, Bjørås M, Wang W, Zhang GY, Han JL, et al. 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.
114. She LY, Sun JF, Xiong L, Li AK, Li LW, Wu HB, et al. Ginsenoside RK1 improves cognitive impairments and pathological changes in Alzheimer's disease *via* stimulation of the AMPK/Nrf2 signaling pathway. *Phytomedicine* 2024;**122**:155168.
115. She LY, Xiong L, Li LW, Zhang J, Sun JF, Wu HB, et al. Ginsenoside Rk3 ameliorates Aβ-induced neurotoxicity in APP/PS1 model mice *via* AMPK signaling pathway. *Biomed Pharmacother* 2023;**158**: 114192.
116. Li TY, Chen JX, Xie ZY, Fang JS, Wu QQ, Cao XY, et al. Ginsenoside Ro ameliorates cognitive impairment and neuroinflammation in APP/PS1 mice *via* the IBA1/GFAP−MAPK signaling pathway. *Front Pharmacol* 2025;**16**:1528590.
117. Choi JH, Jang M, Nah SY, Oh S, Cho IH. Multitarget effects of Korean Red Ginseng in animal model of Parkinson's disease: anti-apoptosis, antioxidant, antiinflammation, and maintenance of blood−brain barrier integrity. *J Ginseng Res* 2018;**42**:379−88.
118. Choi JH, Jang M, Oh S, Nah SY, Cho IH. Multi-target protective effects of gintonin in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-mediated model of Parkinson's disease *via* lysophosphatidic acid receptors. *Front Pharmacol* 2018;**9**:515.
119. Shi DD, Huang YH, Lai CSW, Dong CM, Ho LC, Li XY, et al. Ginsenoside Rg1 prevents chemotherapy-induced cognitive impairment: associations with microglia-mediated cytokines, neuroinflammation, and neuroplasticity. *Mol Neurobiol* 2019;**56**:5626−42.
120. Liu JQ, Zhao M, Zhang Z, Cui LY, Zhou X, Zhang W, et al. Rg1 improves LPS-induced Parkinsonian symptoms in mice *via* inhibition

of NF-κB signaling and modulation of M1/M2 polarization. *Acta Pharmacol Sin* 2020;**41**:523−34.
121. He H, Xie XF, Kang XX, Zhang JQ, Wang L, Hu N, et al. Ginsenoside Rg1 ameliorates depressive-like behavior by inhibiting NLRP3 inflammasome activation in mice exposed to chronic stress. *Eur J Pharmacol* 2023;**960**:176120.
122. Dong YX, Chu SF, Wang SS, Tian YJ, He WB, Du YS, et al. Rg1 exerts protective effect in CPZ-induced demyelination mouse model *via* inhibiting CXCL10-mediated glial response. *Acta Pharmacol Sin* 2022;**43**:563−76.
123. Hiramatsu G, Matsuda K, Uta D, Mihara K, Kume T. Panaxytriol inhibits lipopolysaccharide-induced microglia activation in brain inflammation *in vivo*. *Biol Pharm Bull* 2021;**44**:1024−8.
124. Park JS, Shin JA, Jung JS, Hyun JW, Van Le TK, Kim DH, et al. Anti-inflammatory mechanism of compound K in activated microglia and its neuroprotective effect on experimental stroke in mice. *J Pharmacol Exp Therapeut* 2012;**341**:59−67.
125. Wang X, Shi YJ, Niu TY, Chen TT, Li HB, Wu SH, et al. Neuroprotective effect of 20 (S) - protopanaxadiol (PPD) attenuates NLRP3 inflammasome-mediated microglial pyroptosis in vascular dementia rats. *Neurosci Lett* 2023;**814**:137439.
126. Park SM, Choi MS, Sohn NW, Shin JW. Ginsenoside Rg3 attenuates microglia activation following systemic lipopolysaccharide treatment in mice. *Biol Pharm Bull* 2012;**35**:1546−52.
127. Zhou TT, Zu G, Wang X, Zhang XG, Li S, Liang ZH, et al. Immunomodulatory and neuroprotective effects of ginsenoside Rg1 in the MPTP(1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) -induced mouse model of Parkinson's disease. *Int Immunopharmacol* 2015;**29**:334−43.
128. Kang A, Xie T, Zhu D, Shan JJ, Di LQ, Zheng X. Suppressive effect of ginsenoside Rg3 against lipopolysaccharide-induced depression-like behavior and neuroinflammation in mice. *J Agric Food Chem* 2017;**65**:6861−9.
129. Li DW, Zhou FZ, Sun XC, Li SC, Yang JB, Sun HH, et al. Ginsenoside Rb1 protects dopaminergic neurons from inflammatory injury induced by intranigral lipopolysaccharide injection. *Neural Regen Res* 2019;**14**:1814−22.
130. Lee JY, Choi HY, Park CS, Pyo MK, Yune TY, Kim GW, et al. GSKG9 ameliorates diabetic neuropathic pain induced by streptozotocin in rats. *J Ginseng Res* 2019;**43**:58−67.
131. Shin EJ, Nguyen BT, Sharma N, Tran NKC, Nguyen YND, Hwang Y, et al. Ginsenoside re mitigates memory impairments in aged GPx-1 KO mice by inhibiting the interplay between PAFR, NFκB, and microgliosis in the hippocampus. *Food Chem Toxicol* 2023;**173**:113627.
132. Choi JH, Lee MJ, Jang M, Kim HJ, Lee S, Lee SW, et al. Panax ginseng exerts antidepressant-like effects by suppressing neuroinflammatory response and upregulating nuclear factor erythroid 2 related factor 2 signaling in the amygdala. *J Ginseng Res* 2018;**42**:107−15.
133. Park JS, Park EM, Kim DH, Jung K, Jung JS, Lee EJ, et al. Anti-inflammatory mechanism of ginseng saponins in activated microglia. *J Neuroimmunol* 2009;**209**:40−9.
134. Niu HZ, Zhang M, Zhang KY, Aishan S, Li H, Wu W. In-depth investigation on potential mechanism of forest-grown ginseng alleviating Alzheimer's disease *via* UHPLC−MS-based metabolomics. *Metabolites* 2025;**15**:93.
135. Zhu JH, Jiang YJ, Wu LY, Lu TT, Xu GL, Liu XF. Suppression of local inflammation contributes to the neuroprotective effect of ginsenoside Rb1 in rats with cerebral ischemia. *Neuroscience* 2012;**202**:342−51.
136. Lee JS, Song JH, Sohn NW, Shin JW. Inhibitory effects of ginsenoside Rb1 on neuroinflammation following systemic lipopolysaccharide treatment in mice. *Phytother Res* 2013;**27**:1270−6.
137. Kumar A, Rinwa P, Dhar H. Microglial inhibitory effect of ginseng ameliorates cognitive deficits and neuroinflammation following traumatic head injury in rats. *Inflammopharmacology* 2014;**22**:155−67.
138. Sun XC, Ren XF, Chen L, Gao XQ, Xie JX, Chen WF. Glucocorticoid receptor is involved in the neuroprotective effect of ginsenoside Rg1 against inflammation-induced dopaminergic neuronal degeneration in substantia nigra. *J Steroid Biochem Mol Biol* 2016;**155**:94−103.
139. Li YJ, Wang F, Luo Y. Ginsenoside Rg1 protects against sepsis-associated encephalopathy through beclin 1-independent autophagy in mice. *J Surg Res* 2017;**207**:181−9.
140. Jiang N, Lv JW, Wang HX, Huang H, Wang Q, Lu C, et al. Ginsenoside Rg1 ameliorates chronic social defeat stress-induced depressive-like behaviors and hippocampal neuroinflammation. *Life Sci* 2020;**252**:117669.
141. Zhang GY, Xia F, Zhang YX, Zhang X, Cao YH, Wang L, et al. Ginsenoside Rd is efficacious against acute ischemic stroke by suppressing microglial proteasome-mediated inflammation. *Mol Neurobiol* 2016;**53**:2529−40.
142. Chen HY, Dong MM, He HH, Piao XM, Han X, Li RX, et al. Ginsenoside re prevents depression-like behaviors *via* inhibition of inflammation, oxidative stress, and activating BDNF/TrkB/ERK/CREB signaling: an *in vivo* and *in vitro* study. *J Agric Food Chem* 2024;**72**:19838−51.
143. Gao XQ, Du ZR, Yuan LJ, Zhang WD, Chen L, Teng JJ, et al. Ginsenoside Rg1 exerts anti-inflammatory effects *via* G protein-coupled estrogen receptor in lipopolysaccharide-induced microglia activation. *Front Neurosci* 2019;**13**:1168.
144. Xu X, Jin L, Jiang T, Lu Y, Aosai F, Piao HN, et al. Ginsenoside Rh2 attenuates microglial activation against toxoplasmic encephalitis *via* TLR4/NF-κB signaling pathway. *J Ginseng Res* 2020;**44**:704−16.
145. Lee YY, Park JS, Lee EJ, Lee SY, Kim DH, Kang JL, et al. 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**:3472−80.
146. Guo Y, Xie JP, Zhang LC, Yang LL, Ma JQ, Bai YF, et al. Ginsenoside Rb1 exerts antidepressant-like effects *via* suppression inflammation and activation of AKT pathway. *Neurosci Lett* 2021;**744**:135561.
147. Madhi I, Kim JH, Shin JE, Kim Y. Ginsenoside re exhibits neuroprotective effects by inhibiting neuroinflammation *via* CAMK/MAPK/NF-κB signaling in microglia. *Mol Med Rep* 2021;**24**:698.
148. Joo SS, Lee DI. Potential effects of microglial activation induced by ginsenoside Rg3 in rat primary culture: enhancement of type A macrophage scavenger receptor expression. *Arch Pharm Res (Seoul)* 2005;**28**:1164−9.
149. Wang N, Yang JY, Chen RJ, Liu YY, Liu SJ, Pan YN, et al. Ginsenoside Rg1 ameliorates Alzheimer's disease pathology *via* restoring mitophagy. *J Ginseng Res* 2023;**47**:448−57.
150. Jing X, Zhao YC, Wang G, Tian WQ. Ginsenoside 1 mitigates postoperative cognitive dysfunction by enhancing microglial Aβ clearance through the endo-lysosomal pathway. *Int Immunopharmacol* 2025;**150**:114281.
151. Hu KC, Ye JR, Fan PL, Zheng RF, Wang SS, Peng Y, et al. Targeting and reprogramming microglial phagocytosis of neutrophils by ginsenoside Rg1 nanovesicles promotes stroke recovery. *Bioact Mater* 2025;**47**:181−97.
152. Zhang LJ, Tang MM, Xie XF, Zhao QY, Hu N, He H, et al. Ginsenoside Rb1 induces a pro-neurogenic microglial phenotype *via* PPARγ activation in male mice exposed to chronic mild stress. *J Neuroinflammation* 2021;**18**:171.
153. Wang D, Zhao SX, Pan JW, Wang Z, Li Y, Xu XX, et al. Ginsenoside Rb1 attenuates microglia activation to improve spinal cord injury *via* microRNA-130b-5p/TLR4/NF-κB axis. *J Cell Physiol* 2021;**236**:2144−55.
154. Li JN, Gao W, Zhao ZH, Li YN, Yang LX, Wei W, et al. Ginsenoside Rg1 reduced microglial activation and mitochondrial dysfunction to alleviate depression-like behaviour *via* the GAS5/EZH2/SOCS3/NRF2 axis. *Mol Neurobiol* 2022;**59**:2855−73.

155. Sui CB, Liu Y, Jiang J, Tang JH, Yu L, Lv GY. Ginsenoside Rg1 ameliorates cerebral ischemia−reperfusion injury by regulating Pink1/Parkin-mediated mitochondrial autophagy and inhibiting microglia NLRP3 activation. *Brain Res Bull* 2024;**216**:111043.
156. Yang X, Chu SF, Wang ZZ, Li FF, Yuan YH, Chen NH. Ginsenoside Rg1 exerts neuroprotective effects in 3-nitropronpionic acid-induced mouse model of Huntington's disease *via* suppressing MAPKs and NF-κB pathways in the striatum. *Acta Pharmacol Sin* 2021;**42**: 1409−21.
157. Ye RD, Yang QZ, Kong XW, Han JL, Zhang X, Zhang YX, et al. Ginsenoside Rd attenuates early oxidative damage and sequential inflammatory response after transient focal ischemia in rats. *Neurochem Int* 2011;**58**:391−8.
158. Xu X, Lu YN, Cheng JH, Lan HW, Lu JM, Jin GN, et al. Ginsenoside Rh2 reduces depression in offspring of mice with maternal toxoplasma infection during pregnancy by inhibiting microglial activation *via* the HMGB1/TLR4/NF-κB signaling pathway. *J Ginseng Res* 2022;**46**:62−70.
159. Jin GN, Lu JM, Lan HW, Lu YN, Shen XY, Xu X, et al. Protective effect of ginsenoside Rh2 against *Toxoplasma gondii* infection-induced neuronal injury through binding TgCDPK1 and NLRP3 to inhibit microglial NLRP3 inflammasome signaling pathway. *Int Immunopharmacol* 2022;**112**:109176.
160. Ren Y, Ye D, Ding YP, Wei N. Ginsenoside Rk1 prevents 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinson's disease *via* activating silence information regulator 3-mediated Nrf2/HO-1 signaling pathway. *Hum Exp Toxicol* 2023;**42**:9603271231220610.
161. Cai M, Yang EJ. Ginsenoside re attenuates neuroinflammation in a symptomatic ALS animal model. *Am J Chin Med* 2016;**44**:401−13.
162. Lee MJ, Jang M, Choi J, Chang BS, Kim DY, Kim SH, et al. Korean red ginseng and ginsenoside-Rb1/-Rg1 alleviate experimental autoimmune encephalomyelitis by suppressing Th1 and Th17 Cells and upregulating regulatory T cells. *Mol Neurobiol* 2016;**53**:1977−2002.
163. Mijan MA, Kim JY, Moon SY, Choi SH, Nah SY, Yang HJ. Gintonin enhances proliferation, late stage differentiation, and cell survival from endoplasmic reticulum stress of oligodendrocyte lineage cells. *Front Pharmacol* 2019;**10**:1211.
164. Nam SM, Choi SH, Cho HJ, Seo JS, Choi M, Nahm SS, et al. Ginseng gintonin attenuates lead-induced rat cerebellar impairments during gestation and lactation. *Biomolecules* 2020;**10**:385.
165. Chen Y, Li YY, Wang S, Zhou T, Chen NH, Yuan YH. Ginsenoside Rg1 plays a neuroprotective role in regulating the iron-regulated proteins and against lipid peroxidation in oligodendrocytes. *Neurochem Res* 2022;**47**:1721−35.
166. Kwon OW, Kim D, Koh E, Yang HJ. Korean red ginseng and Rb1 facilitate remyelination after cuprizone diet-induced demyelination. *J Ginseng Res* 2023;**47**:319−28.
167. Lee A, Kwon OW, Jung KR, Song GJ, Yang HJ. The effects of Korean Red Ginseng-derived components on oligodendrocyte lineage cells: distinct facilitatory roles of the non-saponin and saponin fractions, and Rb1, in proliferation, differentiation and myelination. *J Ginseng Res* 2022;**46**:104−14.
168. Lee MJ, Choi JH, Kwon TW, Jo HS, Ha Y, Nah SY, et al. Korean red ginseng extract ameliorates demyelination by inhibiting infiltration and activation of immune cells in cuprizone-administrated mice. *J Ginseng Res* 2023;**47**:672−80.
169. Choi JH, Oh J, Lee MJ, Ko SG, Nah SY, Cho IH. Gintonin mitigates experimental autoimmune encephalomyelitis by stabilization of Nrf2 signaling *via* stimulation of lysophosphatidic acid receptors. *Brain Behav Immun* 2021;**93**:384−98.
170. Zhu DL, Liu M, Yang YW, Ma LL, Jiang Y, Zhou LL, et al. Ginsenoside Rd ameliorates experimental autoimmune encephalomyelitis in C57BL/6 mice. *J Neurosci Res* 2014;**92**:1217−26.
171. Nam SM, Choi JH, Choi SH, Cho HJ, Cho YJ, Rhim H, et al. Ginseng gintonin alleviates neurological symptoms in the G93A-SOD1 transgenic mouse model of amyotrophic lateral sclerosis through lysophosphatidic acid 1 receptor. *J Ginseng Res* 2021;**45**: 390−400.
172. Kim H, Moon S, Lee D, Park J, Kim CH, Kim YM, et al. Korean red ginseng-induced SIRT3 promotes the Tom22-HIF-1α circuit in normoxic astrocytes. *Cells* 2023;**12**:1512.
173. Kim M, Kim J, Moon S, Choi BY, Kim S, Jeon HS, et al. Korean red ginseng improves astrocytic mitochondrial function by upregulating HO-1-mediated AMPKα-PGC-1α-ERRα circuit after traumatic brain injury. *Int J Mol Sci* 2021;**22**:13081.
174. Kim M, Moon S, Jeon HS, Kim S, Koh SH, Chang MS, et al. Dual effects of Korean red ginseng on astrocytes and neural stem cells in traumatic brain injury: the HO-1-Tom20 axis as a putative target for mitochondrial function. *Cells* 2022;**11**:892.
175. Shin SJ, Jeon SG, Kim JI, Jeong YO, Kim S, Park YH, et al. Red ginseng attenuates Aβ-induced mitochondrial dysfunction and Aβ-mediated pathology in an animal model of Alzheimer's disease. *Int J Mol Sci* 2019;**20**:3030.
176. Jang M, Choi JH, Chang Y, Lee SJ, Nah SY, Cho IH. Gintonin, a ginseng-derived ingredient, as a novel therapeutic strategy for Huntington's disease: activation of the Nrf2 pathway through lysophosphatidic acid receptors. *Brain Behav Immun* 2019;**80**:146−62.
177. Lee JY, Choi HY, Park CS, Kim DH, Yune TY. Total saponin extract, ginsenoside Rb1, and compound K alleviate peripheral and central neuropathic pain through estrogen receptors on rats. *Phytother Res* 2021;**35**:2119−32.
178. Lee JY, Park CS, Choi HY, Yune TY. Ginseng extracts, GS-KG9 and GS-E3D, prevent blood−brain barrier disruption and thereby inhibit apoptotic cell death of hippocampal neurons in streptozotocin-induced diabetic rats. *Nutrients* 2020;**12**:2383.
179. Lee MJ, Chang BJ, Oh S, Nah SY, Cho IH. Korean red ginseng mitigates spinal demyelination in a model of acute multiple sclerosis by downregulating p38 mitogen-activated protein kinase and nuclear factor-κB signaling pathways. *J Ginseng Res* 2018;**42**:436−46.
180. Xu T, Shen XF, Yu HL, Sun LL, Lin WH, Zhang CX. Water-soluble ginseng oligosaccharides protect against scopolamine-induced cognitive impairment by functioning as an antineuroinflammatory agent. *J Ginseng Res* 2016;**40**:211−9.
181. Kim KW, Lee YS, Choi BR, Yoon D, Lee DY. Anti-neuroinflammatory effect of the ethanolic extract of black ginseng through TLR4-MyD88-regulated inhibition of NF-κB and MAPK signaling pathways in LPS-induced BV2 microglial cells. *Int J Mol Sci* 2023; **24**:15320.
182. Liu L, Vollmer MK, Fernandez VM, Dweik Y, Kim H, Doré S. Korean red ginseng pretreatment protects against long-term sensorimotor deficits after ischemic stroke likely through Nrf2. *Front Cell Neurosci* 2018;**12**:74.
183. Liu L, Vollmer MK, Ahmad AS, Fernandez VM, Kim H, Doré S. Pretreatment with Korean red ginseng or dimethyl fumarate attenuates reactive gliosis and confers sustained neuroprotection against cerebral hypoxic-ischemic damage by an Nrf2-dependent mechanism. *Free Radic Biol Med* 2019;**131**:98−114.
184. Liu L, Kelly MG, Wierzbicki EL, Escober-Nario IC, Vollmer MK, Doré S. Nrf2 plays an essential role in long-term brain damage and neuroprotection of Korean Red Ginseng in a permanent cerebral ischemia model. *Antioxidants* 2019;**8**:273.
185. Shin EJ, Shin SW, Nguyen TT, Park DH, Wie MB, Jang CG, et al. Ginsenoside re rescues methamphetamine-induced oxidative damage, mitochondrial dysfunction, microglial activation, and dopaminergic degeneration by inhibiting the protein kinase Cδ gene. *Mol Neurobiol* 2014;**49**:1400−21.
186. Xu KN, Zhang YF, Wang Y, Ling P, Xie X, Jiang CY, et al. Ginseng Rb fraction protects glia, neurons and cognitive function in a rat model of neurodegeneration. *PLoS One* 2014;**9**:e101077.
187. Liu L, Vollmer MK, Kelly MG, Fernandez VM, Fernandez TG, Kim H, et al. Reactive gliosis contributes to Nrf2-dependent neuroprotection by pretreatment with dimethyl fumarate or Korean red ginseng against hypoxic-ischemia: focus on hippocampal injury. *Mol Neurobiol* 2020;**57**:105−17.
188. Jeon H, Bae CH, Lee Y, Kim HY, Kim S. Korean red ginseng suppresses 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced

inflammation in the substantia nigra and colon. *Brain Behav Immun* 2021;**94**:410−23.
189. Hou J, Jeon B, Baek J, Yun Y, Kim D, Chang B, et al. High fat diet-induced brain damaging effects through autophagy-mediated senescence, inflammation and apoptosis mitigated by ginsenoside F1-enhanced mixture. *J Ginseng Res* 2022;**46**:79−90.
190. Zhu P, Samukawa K, Fujita H, Kato H, Sakanaka M. Oral administration of red ginseng extract promotes neurorestoration after compressive spinal cord injury in rats. *Evid Based Complement Alternat Med* 2017;**2017**:1265464.
191. Yan L, Hu Q, Mak MS, Lou J, Xu SL, Bi CW, et al. A Chinese herbal decoction, reformulated from Kai-Xin-San, relieves the depression-like symptoms in stressed rats and induces neurogenesis in cultured neurons. *Sci Rep* 2016;**6**:30014.
192. Qu SC, Liu MQ, Cao C, Wei CQ, Meng XE, Lou QY, et al. Chinese medicine formula kai-xin-san ameliorates neuronal inflammation of CUMS-induced depression-like mice and reduces the expressions of inflammatory factors *via* inhibiting TLR4/IKK/NF-κB pathways on BV2 cells. *Front Pharmacol* 2021;**12**:626949.
193. Lu J, Tang XL, Zhang YX, Chu HB, Jing CX, Wang YF, et al. Exploring the molecular mechanism of Yinao Fujian formula on ischemic stroke based on network pharmacology and experimental verification. *Heliyon* 2024;**10**:e23742.
194. Cai M, Shin BY, Kim DH, Kim JM, Park SJ, Park CS, et al. Neuroprotective effects of a traditional herbal prescription on transient cerebral global ischemia in gerbils. *J Ethnopharmacol* 2011;**138**: 723−30.
195. Wang HQ, Yang SW, Gao Y, Liu YJ, Li X, Ai QD, et al. Novel antidepressant mechanism of ginsenoside Rg1: regulating biosynthesis and degradation of connexin43. *J Ethnopharmacol* 2021;**278**: 114212.
196. Rahman MA, Hwang H, Nah SY, Rhim H. Gintonin stimulates autophagic flux in primary cortical astrocytes. *J Ginseng Res* 2020; **44**:67−78.
197. Choi SH, Kim HJ, Cho HJ, Park SD, Lee NE, Hwang SH, et al. Gintonin, a ginseng-derived exogenous lysophosphatidic acid receptor ligand, protects astrocytes from hypoxic and re-oxygenation stresses through stimulation of astrocytic glycogenolysis. *Mol Neurobiol* 2019;**56**:3280−94.
198. Choi SH, Kim HJ, Cho HJ, Park SD, Lee NE, Hwang SH, et al. Gintonin-mediated release of astrocytic vascular endothelial growth factor protects cortical astrocytes from hypoxia-induced cell damages. *J Ginseng Res* 2019;**43**:305−11.
199. Ko HM, Joo SH, Kim P, Park JH, Kim HJ, Bahn GH, et al. Effects of Korean Red Ginseng extract on tissue plasminogen activator and plasminogen activator inhibitor-1 expression in cultured rat primary astrocytes. *J Ginseng Res* 2013;**37**:401−12.
200. Hiramatsu G, Uta D, Mihara K, Andoh T, Kume T. Inhibitory effect of panaxytriol on BV-2 microglial cell activation. *J Pharmacol Sci* 2021;**145**:273−8.
201. Yan XJ, Bai X, Sun GH, Duan ZG, Fu RZ, Zeng W, et al. Ginsenoside compound K alleviates brain aging by inhibiting ferroptosis through modulation of the ASK1-MKK7-JNK signaling pathway. *Phytomedicine* 2024;**135**:156239.
202. Lee BC, Choe YM, Suh GH, Choi IG, Kim HS, Hwang J, et al. Ginseng intake and Alzheimer disease-specific cognition in older adults according to apolipoprotein ϵ4 allele status. *Front Aging Neurosci* 2023;**15**:1152626.
203. Heo JH, Lee ST, Oh MJ, Park HJ, Shim JY, Chu K, et al. Improvement of cognitive deficit in Alzheimer's disease patients by long term treatment with Korean Red Ginseng. *J Ginseng Res* 2011; **35**:457−61.
204. Liu X, Xia JL, Wang L, Song Y, Yang J, Yan Y, et al. Efficacy and safety of ginsenoside-Rd for acute ischaemic stroke: a randomized, double-blind, placebo-controlled, phase II multicenter trial. *Eur J Neurol* 2009;**16**:569−75.
205. Liu X, Wang L, Wen AD, Yang J, Yan Y, Song Y, et al. Ginsenoside-Rd improves outcome of acute ischaemic stroke — a randomized, double-blind, placebo-controlled, multicenter trial. *Eur J Neurol* 2012;**19**:855−63.
206. Lee KH, Bahk WM, Lee SJ, Pae CU. Effectiveness and tolerability of Korean red ginseng augmentation in Major depressive disorder patients with difficult-to-treat in routine practice. *Clin Psychopharmacol Neurosci* 2020;**18**:621−6.
207. Song SW, Kim HN, Shim JY, Yoo BY, Kim DH, Lee SH, et al. Safety and tolerability of Korean red ginseng in healthy adults: a multicenter, double-blind, randomized, placebo-controlled trial. *J Ginseng Res* 2018;**42**:571−6.
208. Lee R, Lee HS, Kim WW, Kim M, Nah SY. Cognitive function improvement effects of gintonin-enriched fraction in subjective memory impairment: an assessor- and participant-blinded placebo-controlled study. *J Ginseng Res* 2023;**47**:735−42.
209. Shin MB, Kim SA, Lee S, Shim WS, Lee KT, Lee SK, et al. Pharmacokinetic comparison of ginsenosides between fermented and non-fermented red ginseng in healthy volunteers. *Pharmaceutics* 2022;**14**:2807.