Review

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Exploring the Neuroprotective Potential of *Astragalus Membranaceus* in Central Nervous System Diseases

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Review

Exploring the Neuroprotective Potential of *Astragalus Membranaceus* in Central Nervous System Diseases

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Abstract

Aim of the work: This review aims to systematically integrate the mechanism of action of *Astragalus membranaceus* and its active components on central nervous system(CNS) diseases, with a focus on exploring its therapeutic potential, and introducing related health food products that use it as an adjunct treatment for CNS diseases.*Materials and methods:* Searches were conducted through the PubMed and Web of Science databases using the keywords "*Astragalus membranaceus*", "*Astragali Radix*", "Astragaloside IV (AS-IV)", "*Astragalus membranaceus* polysaccharides (APS)" and "CNS diseases". Reports on the effects of *Astragalus membranaceus* and its components on CNS diseases were identified and reviewed.*Results:* This review provides a comprehensive summary of the latest research advancements concerning *Astragalus membranaceus* across several pivotal domains, including its extensive historical usage, active constituents, pharmacological properties, potential therapeutic applications for CNS disorders, safety profile, contemporary formulations, and significant findings in the realm of health food applications. The medicinal history of *Astragalus membranaceus* membranaceus is both long-standing and profound, with usage spanning over 2,000 years. Its active components, such as AS-IV and APS, have demonstrated considerable therapeutic efficacy in the treatment of CNS diseases. The pharmacological effects of *Astragalus membranaceus* membranaceus are diverse, encompassing anti-neuroinflammatory, anti-oxidative stress, anti-apoptotic activities, modulation of autophagy, anti-ferroptotic effects, and protection of the blood-brain barrier. Furthermore, the practical applications of *Astragalus membranaceus* extend beyond the medical field, encompassing modern pharmaceutical preparations and health food products, among other areas. Despite the promising potential of *Astragalus membranaceus* in the treatment of CNS diseases, numerous challenges persist in the comprehensive investigation of its pharmacological mechanisms and the standardization of its quality. Nonetheless, *Astragalus membranaceus* occupies an essential and significant role in the management of CNS disorders and is anticipated to have an increasingly prominent impact in related fields in the future.*Conclusion: Astragalus membranaceus* has emerged as a promising pharmacological agent in the global health sector, attributed to its notable efficacy in addressing CNS disorders. Combining traditional knowledge with innovative research and based on the concept of "homology of medicine and food", the application of *Astragalus membranaceus* as an auxiliary therapy in the field of health food fully leverages its neuroprotective and anti-inflammatory properties, which is an important direction for future research.

Keywords: *Astragalus membranaceus*; active ingredient; central nervous system diseases; mechanism of action; homology of medicine and food

1. Introduction

CNS disorders continue to climb up the global burden of disease list, and it has been reported that the number of deaths in 2019 alone is as high as 10 million(Ding et al., 2022). For instance, the

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occurrence of neurodegenerative diseases like PD continues to rise annually, leading to patient distress(Song et al., 2023; Zhong & Zhu, 2022). The severity of CNS disease is not only reflected in the direct destruction of neurological function, but also in the chain reaction of multiple systems. For instance, hepatic encephalopathy, a severe issue associated with advanced liver disease, can quickly result in reduced consciousness, coma, and potentially death(Wijdicks, 2016). These conditions not only endanger individuals' lives and health but also impose a significant burden on society and families due to their high rates of disability and long-term care needs(Jiang et al., 2025). Hence, patients with CNS disorders are in urgent need of novel therapeutic approaches. Given their origin from natural resources and low toxicity, TCM have gradually gained wide recognition in the preventive and therapeutic fields.

Astragalus membranaceus membranaceus (Fisch.) Bge. var. Mongholicus (Bge.)(Li et al., 2022a), is renowned as "the holy medicine" for enhancing qi. First mentioned in Shennong Ben Cao Jing (Shi, Shi, Zhao, Ma, & Zhang, 2024), it has a long history of medicinal use and is one of the most commonly used TCM for CNS disorders (Figure 1) (Abd Elrahim Abd Elkader, Essawy, & Al-Shami, 2022). Recent pharmacological research indicates that *Astragalus membranaceus* offers therapeutic benefits through multiple targets and pathways for preventing and treating CNS diseases, due to its diverse active components. Until now, researchers have identified more than 200 compounds from *Astragalus membranaceus*, comprising polysaccharides, saponins, flavonoids, alkaloids, among others, which are like a treasure trove of structurally diverse and functionally rich natural small molecules(Gong et al., 2018). Among them, AS-IV, APS, and Astragaloside total flavonoids have attracted the most attention because of their outstanding biological activities, which together constitute the "main force" of Astragaloside in exerting therapeutic and pharmacological effects(Li et al., 2022b). AS-IV, a form of Astragaloside AST, is vital for its anti-inflammatory and neuroprotective properties by inhibiting NF-κB and other pathways(Yang et al., 2025). CAG is a potent derivative of AS-IV, known for its ability to reduce inflammation and improve lipid metabolism(Weng et al., 2025). APS is a water-soluble, chemically intricate heteropolysaccharide that includes portions of heteropolysaccharides, glucans, and both neutral and acidic polysaccharides, and it has notable effects on modulating immune cell activity.(Liu et al., 2021; Zheng et al., 2020). These representative active ingredients collaborate with each other and together carry the scientific basis for the overall efficacy of *Astragalus membranaceus*.

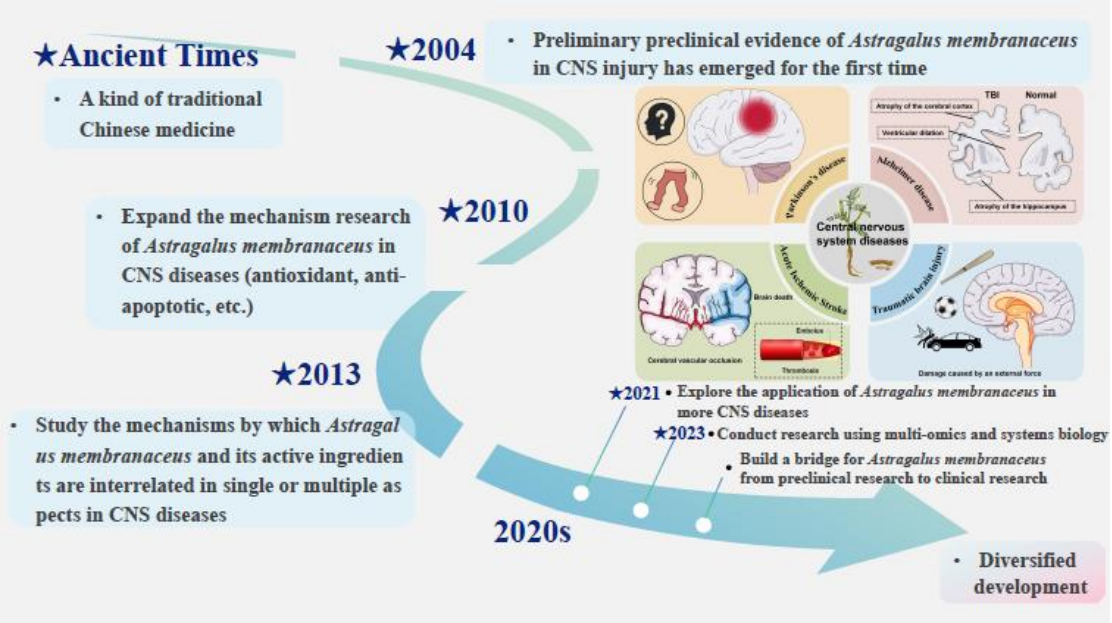

Figure 1. *Astragalus membranaceus* as a treatment option for central nervous system disorders.

Currently, the body of research concerning *Astragalus membranaceus* remains relatively sparse, with a notable absence of systematic reviews addressing its role and potential mechanisms in CNS

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disorders. Consequently, this study seeks to conduct a comprehensive review of the active constituents of *Astragalus membranaceus* and elucidate their molecular mechanisms in the context of CNS disease treatment. The findings aim to furnish novel insights and references for future investigations into *Astragalus membranaceus* and to inform the development of innovative strategies for the prevention and management of CNS disorders.

2. Methods

2.1. Literature Search

PubMed and Web of Science were searched for reports on the effects of *Astragalus membranaceus* and its components on CNS diseases using the following search keywords: "*Astragalus membranaceus*","Astragali Radix","AS-IV","APS","CNS diseases",and "pharmacology". The search period was from database inception through July 2025.

2.2. Inclusion Criteria

The inclusion criteria encompassed studies focusing on *Astragalus membranaceus* and its active constituents in relation to CNS disorders, including AD, TBI, PD, and SCI, as well as pharmacological investigations of *Astragalus membranaceus*.

2.3. Exclusion Criteria

Studies that were duplicates, incomplete, lacked ethical approval, were presented as conference abstracts, appeared as brief newsletters, or were published in languages other than English were excluded.

2.4. Results

Two researchers independently searched keywords and screened titles, abstracts, and full texts based on inclusion and exclusion criteria, resulting in 218 eligible publications. See Figure 2 for the search and screening flowchart.

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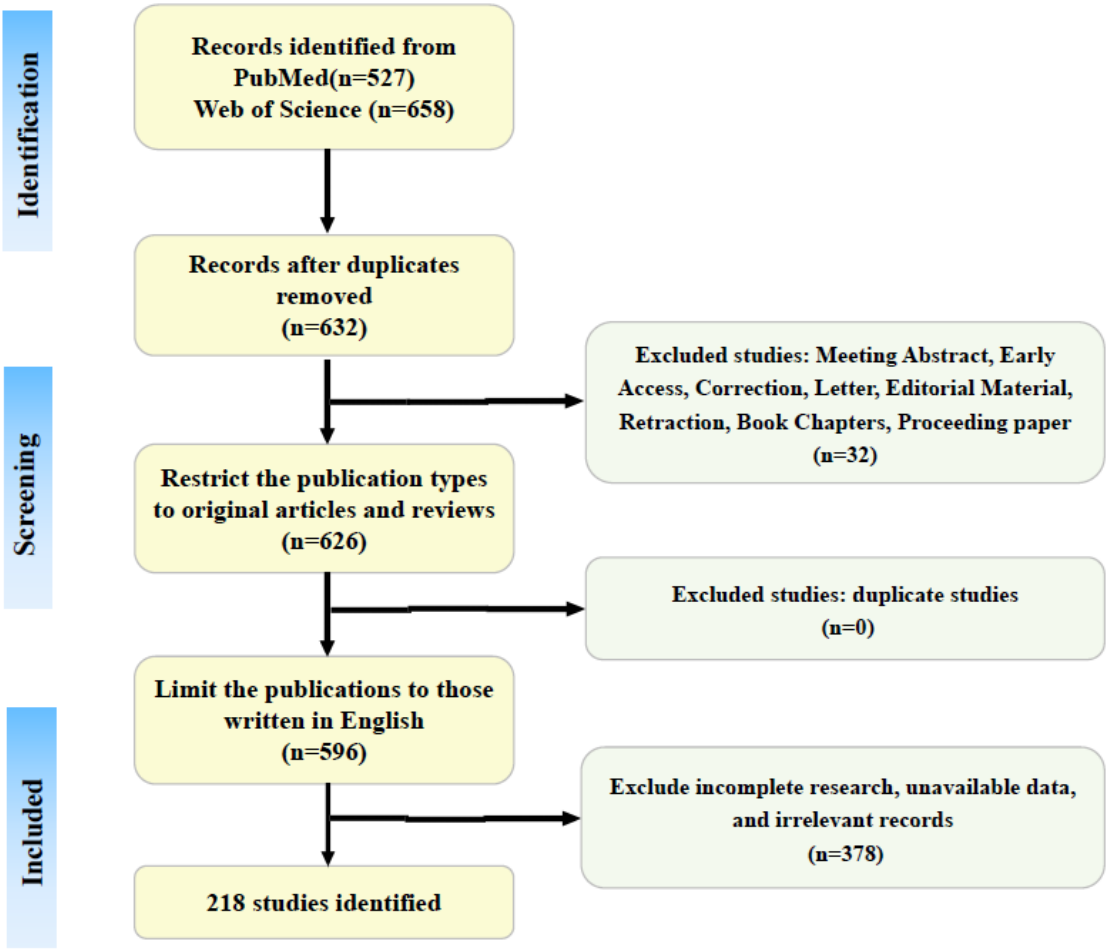

Figure 2. The literature search and screening flowchart.

3. Impact of Astragalus Membranaceus and Its Active Components on the Cns

3.1. Anti-Neuroinflammation

Neuroinflammation is a key pathogenetic mechanism in many CNS diseases, such as CI, SCI, and AD. It has long since ceased to be a "bystander" to CNS disease and is one of the central mechanisms driving disease onset, progression, and determining prognosis(Rathod et al., 2023). One of the major causes of neuroinflammation is the activation of microglia(Cherry, Olschowka, & O'Banion, 2014). When tissues are inflamed, macrophages of the activated M1 phenotype will secrete inflammatory and chemotactic proteins in order to help the host resist the infection and transform into the activated M2 phenotype to repair the damaged tissues(Ruan et al., 2024; Yunna, Mengru, Lei, & Weidong, 2020). NF-κB acts as a key transcriptional regulator in the inflammatory response(Haftcheshmeh et al., 2022), and upon activation, it enhances the secretion of pro-inflammatory molecules like IL-6, IL-8, TNF-α, IL-1β, COX-2, and iNOS, thus intensifying the inflammatory cascade(Tak & Firestein, 2001). NLRP3, a coreceptor in inflammatory vesicles, is linked to inflammation in various CNS disorders and can trigger local and systemic inflammatory responses. Inhibiting NLRP3 can significantly reduce inflammation and protect the CNS (Figure 3)(Coll, Schroder, & Pelegrin, 2022; Kodi, Sankhe, Gopinathan, Nandakumar, & Kishore, 2024).

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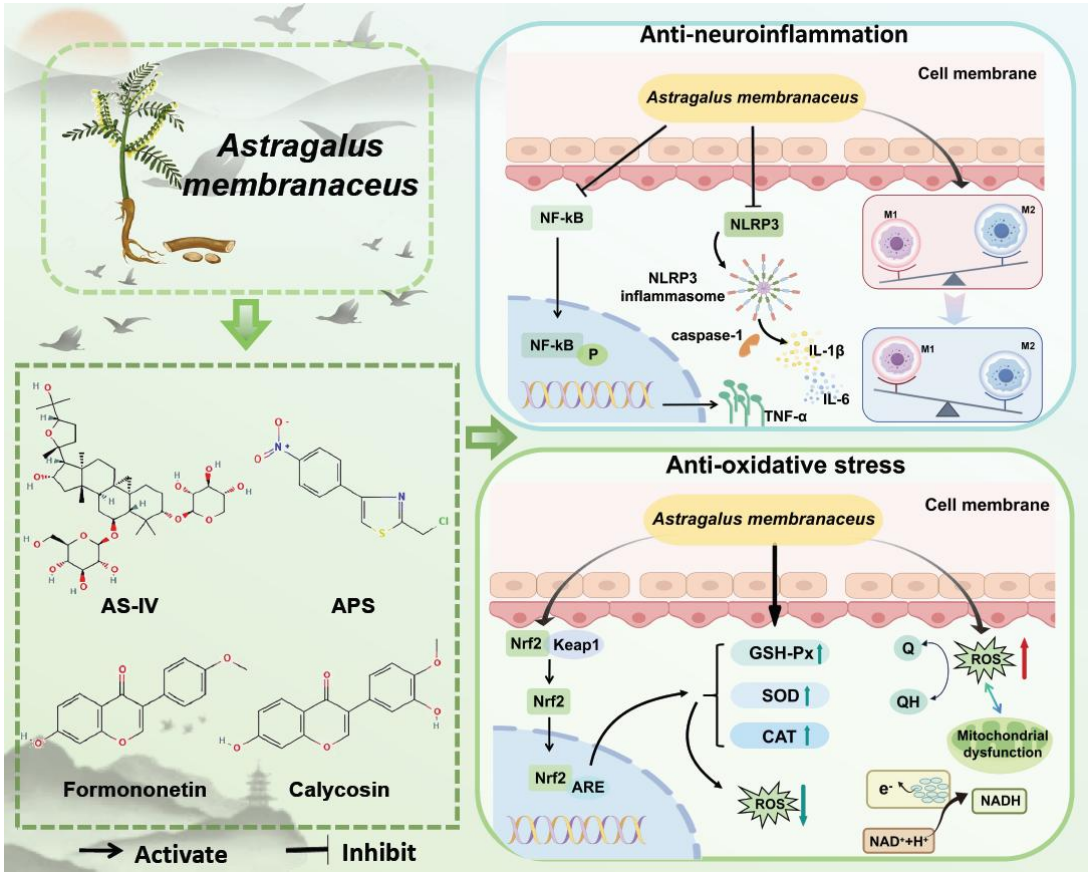

Figure 3. *Astragalus membranaceus* exerts anti-inflammatory and antioxidant stress effects.

3.1.1. Regulatory Effects of Astragalus Membranaceus Components (as-Iv, Aps) on Microglia/Macrophages

Preventing the overactivation of microglia is anticipated to create new treatment options for various neurological disorders. AS-IV has been identified as a possible neuroprotective and anti-inflammatory compound for CNS disorders. In a mouse model of cerebral ischemia, AS-IV demonstrated anti-inflammatory properties by converting microglia/macrophages from the M1 to the M2 phenotype through a mechanism dependent on PPARγ(Li et al., 2021; Mao, Zhao, & Sun, 2025). It simultaneously decreases pro-inflammatory elements like IL-1β, IL-6, TNF-α, MyD88, NF-κB, and TLR4, while boosting anti-inflammatory components such as ARG-1, CD206, and IL-10(Yu et al., 2019, 2023). APS also reverses M1/M2 polarization, promotes ATP degradation to release anti-inflammatory factors, and inhibits P2X7R expression, providing neuroprotection in the cerebral cortex of MCAO rats(Jia et al., 2022; Kong et al., 2024).

3.1.2. Inhibitory Effect of as-Iv on Nlrp3 Inflammatory Body and Related Damage

NLRP3 levels were notably increased in brain tissues affected by hypoxic-ischemic conditions, and its overexpression exacerbated the degree of brain tissue damage, and inhibition of its activity became an important way to protect the CNS(Yang, Wang, Kouadir, Song, & Shi, 2019). In the rat MCAO/R model, AS-IV decreased LOC102555978 expression to lessen cerebral infarction volume and suppress inflammation and cell death.(Gao et al., 2024). Furthermore, in a mouse model of depression caused by RRS and LPS, AS-IV administration significantly increased GSK3β phosphorylation and inhibited NLRP3 inflammatory vesicles, and decreased the levels of inflammatory factors, such as TNF-α and IL-1β(SONG et al., 2018). The combination of AS-IV and hydroxy safflower yellow A treatment in ischemic brain showed a significant increase in NLRP3/ASC/IL-1β/Caspase- 1/GSDMD protein expression, which was significantly more

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pronounced, indicating that the combination suppressed NLRP3 inflammasome-mediated cellular pyroptosis, reduced the inflammatory response, and mitigated brain tissue damage(Hou et al., 2024).

3.1.3. Regulatory Effect of Astragalus Membranaceus on Astrocytes

Astrocytes are the "igniters, amplifiers, and regulators" of the immune cascade in a variety of human CNS diseases(Souza, Almeida, Souza, & Zimmer, 2019). Research conducted in vitro has revealed that activated astrocytes produce high levels of inflammatory mediators, including IL-1β and TNF-α(Tujula et al., 2025; Wang et al., 2021). AS-IV significantly inhibited penicillin-induced expression of inflammatory factors and p-MAPK family proteins in astrocytes, and significantly alleviated neurological damage in epileptic mice(Zhu et al., 2018). AS-IV also inhibited the senescence of astrocytes and prevented dopaminergic neuronal damage in PD by promoting mitochondrial autophagy—degeneration of dopaminergic neurons in PD, showing significant therapeutic potential(Xia, Xie, Ding, Du, & Hu, 2020). APS protects astrocytes from OGD/R-induced neuroinflammation to a certain extent by blocking the HMGB1/RAGE/NF-κB/NLRP3 signaling pathway(Li et al., 2023).

3.1.4. Regulatory Effect of Astragalus Membranaceus on Neutrophils

Neutrophils are integral components of the innate immune system, serving as the initial responders to sites of tissue injury or pathogen invasion, where they participate in the inflammatory response(Xiao et al., 2023). This characteristic underlies their extensive infiltration and activation within brain tissue during the inflammatory response to cerebral ischemia/reperfusion. Consequently, inhibiting this pathway may offer effective protection against CNS diseases(Hagemann et al., 2020). AS-IV mitigates the accumulation of neutrophils in the brain parenchyma by reducing the concentration of MPOs in brain tissue, the percentage of CD11b/CD18-positive neutrophils, and neutrophil-associated molecules in brain tissue up to 24 hours post-reperfusion, thereby enhancing neurological outcomes. This reduction in accumulation within the brain parenchyma contributes to improved neurological outcomes and decreased infarct volume(Li et al., 2012).

3.1.5. Regulatory Effects of Astragalus Membranaceus Through Multiple Inflammatory Signaling Pathways

Signaling pathways associated with inflammation are vital in the onset and advancement of neurological disorders. In the context of TBI, AS-IV significantly contributes to minimizing neuroinflammation and brain damage by downregulating the expression of inflammatory markers IL-6, IL-1β, and TNF-α through the PERK pathway(Zhao et al., 2024). Moreover, addressing PERK-mediated stress in the endoplasmic reticulum lessens neuroinflammation and improves depressive-like symptoms(Xu et al., 2022).In the PC12 neuronal inflammation model induced by 1 mg/mL LPS, AS-IV pretreatment significantly lowered TNF-α, IL-1β, and TLR4 levels and inhibited the IL-17 signaling pathway(Li et al., 2024). APS also suppresses TNF-α, IL-1β, and TLR4 through the NF-κB and MAPK (ERK, JNK) pathways.(Chen et al., 2023).

3.2. Anti-Oxidative Stress

Oxidative stress is characterized by the disruption of cellular mitochondria and the endoplasmic reticulum due to damaging stimuli, leading to the excessive production of ROS and RNS(Dai et al., 2023). This disruption disturbs the balance between oxidative and antioxidant systems, resulting in the accumulation of oxidative products and a decrease in reductase activity. This series of events ultimately triggers the peroxidation of DNA/RNA, proteins, and lipids, as well as tissue damage, culminating in a pathological state(Liu et al., 2015a; Sirnonian & Coyle, 1996; Teleanu et al., 2022). Numerous studies have demonstrated that ROS levels are significantly elevated in the pathophysiology of conditions such as glioma, AIS, AD, and TBI, among others. Common types of

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ROS include H_2O_2, -OH, and O^{2-}(Liu et al., 2023). Maintaining moderate levels of reactive oxygen species during neuronal development is essential for executing critical physiological functions and participating in complex signaling processes (Figure 3)(Jomova et al., 2023).

3.2.1. Astragalus Membranaceus Regulates the Expression Levels of Antioxidant Enzymes

In CNS, SOD and GSH-Px are crucial, with SOD converting superoxide anion to H_2O_2 and GSH-Px further converting H_2O_2 to H_2O and O_2, thereby scavenging ROS and free radicals and attenuating CNS oxidative stress damage. Increasingly accumulating evidence suggests that AS-IV is able to improve the operations of SOD and GSH-Px while reducing the accumulation of oxidative products such as ROS in CNS disease models such as ischemia-reperfusion and experimental autoimmune encephalomyelitis, thereby exerting its biological effects against lipid peroxidation(He et al., 2014, 2013; Liu et al., 2015b; Shao et al., 2014; Yao et al., 2024; Zhang et al., 2012). In addition to the above results, AS-IV reduced the expression of NOX2/4 and increased the T-AOC in the brain tissues of AIS mice(Xu et al., 2018). CA, a flavonoid component of *Astragalus membranaceus*, showed potential neuroprotective effects by decreasing the expression of MDA, NO, and LDH and inhibiting oxidative stress in a SCI model in combination with rehabilitation training(Li, Huan, Jiang, He, & Gao, 2024, 2024).

3.2.2. The Regulation of Mitochondrial Function by Astragalus Membranaceus

Abnormal mitochondrial function is regarded as a central causative factor of oxidative stress(Biala, Dhingra, & Kirshenbaum, 2015)，and an intrinsic key factor driving a series of complex pathological alterations, which play a pivotal role in the process of neurological injury, ionic homeostasis imbalance, and impaired nerve regeneration(Zhao et al., 2019). *Astragalus membranaceus* and its active ingredients have been shown to have significant potential to modulate various mitochondrial functions. AS-IV regulates mitochondrial permeability transition, upregulates Bc1-2 levels, inhibits Caspase-3 activation, and attenuates neurological damage caused by AD, among others(Sun et al., 2014). The extract from *Astragalus membranaceus* root can counteract oxidative damage in the brain tissue of epileptic mice caused by PTZ by enhancing mitochondrial complex activity and membrane potential, thereby providing anticonvulsant effects.(Aldarmaa et al., 2010).

3.2.3. Nrf2 Plays a Core Role in the Antioxidant Stress Resistance of Astragalus Membranaceus

Nrf2 is a key transcription factor regulating antioxidant enzyme genes, crucial for cellular defense against oxidative damage. It binds to Keap1, enters the nucleus, and activates genes like HO-1 and SOD(Bahar, Kim, & Yoon, 2017; Gupta, Ganguly, Rozanas, Stuehr, & Panda, 2016; Silva-Islas & Maldonado, 2018). Activating Nrf2 may offer new treatments for neurological disorders. AS-IV shields cortical neurons from OGD/R damage through the activation of EGFR-Nrf2 signaling(Gu et al., 2015). AS-IV protects neurons from OGD/R damage via EGFR-Nrf2 signaling and, with Rg1, activates the Nrf2/HO-1 pathway to combat oxidative stress(Huang et al., 2014). Studies suggest that FMN, an isoflavonoid in *Astragalus membranaceus*, offers neuroprotection by increasing Nrf2 expression in rats suffering from TBI(Berry et al., 2009; Engler-Chiurazzi, Brown, Povroznik, & Simpkins, 2017)，thereby regulating redox homeostasis. Interestingly, the Chinese herbal formula HGWD reduced oxaliplatin-induced neurotoxicity, mainly by controlling antioxidant precursors and essential molecules in the PI3K/Akt-Nrf2 pathway, which subsequently reduced the oxidative response triggered by paclitaxel in CNS(Lv et al., 2021).

3.3. Anti-Apoptosis

Apoptosis is a self-initiated cell death process triggered by normal cells in both physiological and pathological states, playing a vital role in sustaining biological balance(Castillo Ferrer, Berthenet, & Ichim, 2021). Genes that control apoptosis can be divided into three groups: pro-apoptotic genes (e.g Fas, Bax, ICE, p53)(Reshi, Wu, Wu, Wang, & Hong, 2016; Zhao et al., 2023)、anti-apoptotic genes

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(e.g bcl-2, EIB, IAP)(Soliman & Nafie, 2023), and genes with bidirectional regulatory functions (e.g., c-myc)(Hoffman & Liebermann, 1998). These genes determine cell fate through a sophisticated network, but it is the caspase cascade that ultimately carries out programmed death, and this pathway is regarded as the common endpoint for the convergence of apoptotic signals(Araya, Soni, Hardy, & Julien, 2021). Upon further study, researchers found that apoptosis, such as in neuronal cells, is at the core of the dramatic decline in neurological function and rapid deterioration of the disease (Figure 4).

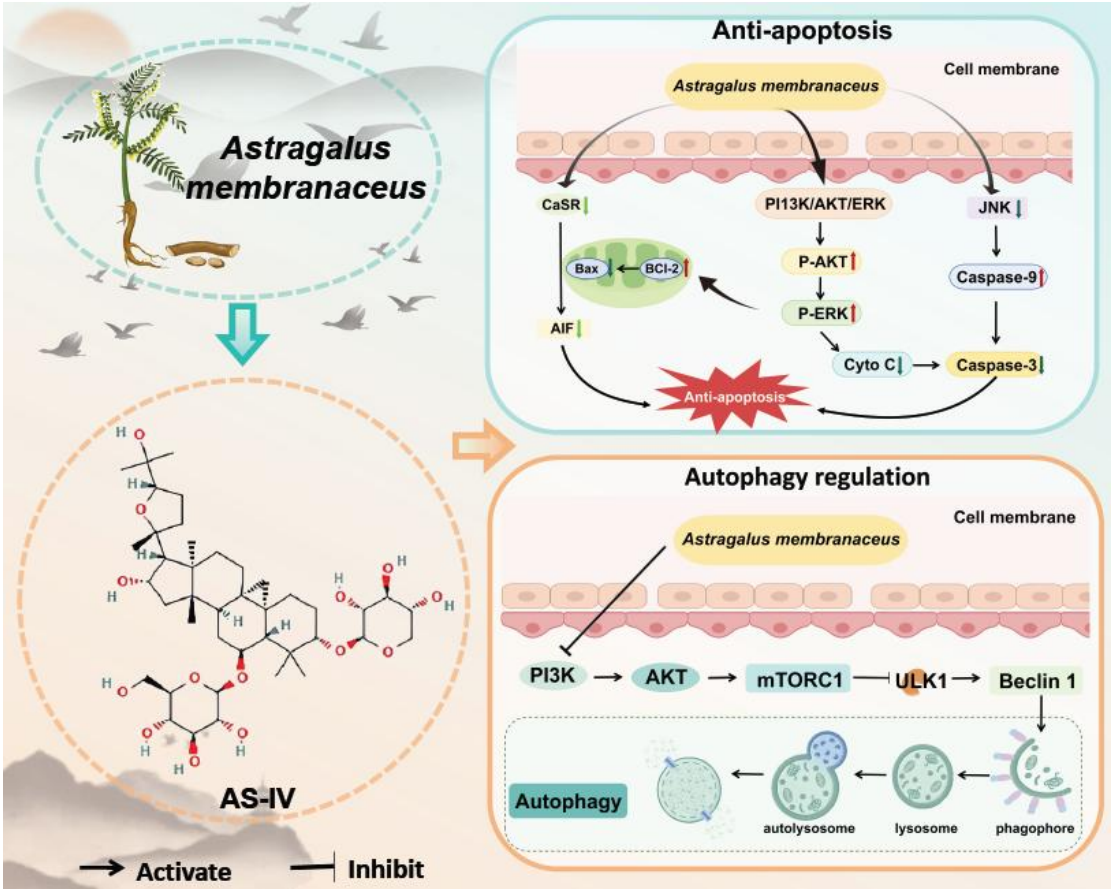

Figure 4. *Astragalus membranaceus* exerts anti-apoptotic and autophagy regulatory effects.

3.3.1. Astragalus Membranaceus Inhibits Jnk Phosphorylation

Activation of JNK leads to the initiation of apoptosis(Thakur et al., 2007). Inhibition of JNK phosphorylation may be one of the key pathways against neuronal apoptosis. AST attenuates neuronal apoptosis in ischemia/reperfusion rats through this mechanism and increases the expression of p-ERK and phosphorylated Akt(Wu, Wu, Gong, Li, & Yin, 2014). Sun's team experimentally verified that AS-IV, administered orally for 3 days, in addition to down-regulating p-JNK and up-regulating p-ERK, p Akt, in addition to down-regulating p-JNK, up-regulating p-ERK, p-ERK, and Klotho, and inhibiting oxidative stress and pro-inflammatory factor release, AS-IV also protects the developing brain from anesthesia-induced neuronal apoptosis(Sun, Chen, Zheng, Zhou, & Ma, 2016).

3.3.2. Astragalus Membranaceus Regulates the Expression of Casr

In CIRI, CaSR is an important G-protein-coupled receptor whose activation exacerbates secondary neurological injury. Increasing evidence suggests that AS-IV inhibits apoptosis and attenuates neurological deficits secondary to CIRI by down-regulating the expression of CaSR and apoptotic proteins such as Fas, FasL, Bid, and Caspase-8. It also attempts to inhibit cleaved caspase-

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3 and upregulate the ratio of Bax/Bcl-2, so the dynamic regulation of CaSR may be one of the targets of AS-IV's action to exert neuroprotective effects and inhibit apoptosis(Du SJ et al., 2021; Yinet al., 2020). AS-IV not only reduces apoptotic protein expression but also inhibits endoplasmic reticulum stress-related proteins like eIF2a, Bip, and CHOP, thereby decreasing cerebral infarction by preventing endothelial cell apoptosis(Hou, Liu, Wu, & Huang, 2020a).

3.3.3. Astragalus Membranaceus Inhibits Apoptosis Through Other Pathways

Research has demonstrated that AS-IV provides anti-apoptotic benefits in the hippocampus of AD rats and boosts cognitive function by lowering Bax and caspase-3 concentrations(Alharbi et al., 2024). Wang et al. discovered that AST suppressed key proteins in the Fas/Fasl-VDAC1 pathway in Aβ1-42-damaged C8D1A cells, reducing apoptosis and enhancing cognitive function in hippocampal astrocytes, which helps alleviate cognitive deficits in AD mice(Wang et al., 2025). Notably, PPARγ is a key molecular switch for the treatment of AD, and its inhibition reduces AβO-induced apoptosis of HT22 cells by AS-IV(Wang et al., 2020).

3.4. Autophagy Regulation

Autophagy maintains cellular balance by removing damaged organelles, faulty proteins, and pathogens through lysosomal degradation and recycling(Debnath, Gammoh, & Ryan, 2023; Xu & Hu, 2022). Numerous studies have demonstrated that abnormalities in autophagy and endolysosomal pathways, associated with neuronal dysfunction, are intricately linked to the pathogenesis of CNS disorders. Consequently, the regulation of autophagy may play a crucial role in the therapeutic strategies for CNS diseases (Figure 4)(Deng, Zhou, Lu, & Yue, 2021; Kapil et al., 2024; Lizama & Chu, 2021).

Astragalus Membranaceus Regulates Autophagy via Ampk and Mtor

AMPK is a crucial energy sensor that helps maintain the balance of cellular energy(Wang, Li, Yuan, Fan, & Cai, 2022). AMPK activity regulates a broad spectrum of metabolic processes, encompassing the modulation of autophagy, mitophagy, and various other mechanisms(Jang et al., 2018). Rapamycin, a principal regulator of cellular metabolism(Deleyto-Seldas & Efeyan, 2021), exerts its inhibitory effects on autophagy by phosphorylating and inactivating critical regulatory proteins, including ULK1, Beclin-1, UVRAG, and TFEB, as well as by suppressing the expression of autophagy-related proteins(Senapati, Mahapatra, Singh, & Bhutia, 2025). Consequently, AMPK and mTOR are posited to play pivotal roles in the regulation of autophagy. Neuronal apoptosis is a major cause of secondary injury after SCI. Research conducted by Lin's team demonstrated that the intraperitoneal administration of AS-IV can induce autophagy in neuronal cells via mTORC1 signaling, thereby conferring protection against apoptosis through the modulation of autophagy. This suggests that AS-IV holds potential as a novel therapeutic agent for SCI(Lin et al., 2020). Researchers found that AST plays a key neuroprotective role by stimulating PI3K/Akt-mTOR pathway-mediated autophagy and upregulating the level of autophagy flux-associated proteins in APP/PS1 mice, which is a new mechanism of AST for treating AD through autophagy regulation(Yang et al., 2023). Hao et al. demonstrated that AS-IV can attenuate autophagy activity by inhibiting the AMPK/mTOR pathway, which subsequently reduces mitochondrial-mediated apoptosis. This action mitigates cellular injury in SH-SY5Y cells and the MCAO model, thereby exerting neuroprotective effects and positioning AS-IV as a potential therapeutic candidate for AIS(Hao, Yang, & Zhu, 2023). Zhang and colleagues identified a novel mechanism for treating I/R injury, wherein AS-IV inhibits apoptosis by enhancing P62-LC3-mediated autophagy and increasing the expression of LC3II/LC3I in HT22 cells following OGD/R treatment. This suggests that the promotion of autophagy regulation by AS-IV represents a new therapeutic mechanism for I/R injury(Zhang et al., 2019). Furthermore, AS-IV modulates the AMPK-MTORC1-ULK pathway to

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enhance autophagy, as evidenced by reduced P-mTOR levels and increased levels of LC3, P-AMPK, and P-ULK in retinal tissues, thereby exerting a therapeutic effect on TON(Sun et al., 2025).

3.5. Anti-Ferroptosis

Ferroptosis is a regulated programmed cell death pathway that results from iron-triggered phospholipid peroxidation(Alves, Lane, Nguyen, Bush, & Ayton, 2025; Hadian & Stockwell, 2020). Since brain tissue is rich in lipids and iron and has a high rate of oxygen consumption, which makes the link to ferroptosis particularly strong, a defense strategy against ferroptosis may be an important tool in the treatment of CNS disease (Figure 5)(Lei, Walker, & Ayton, 2025).

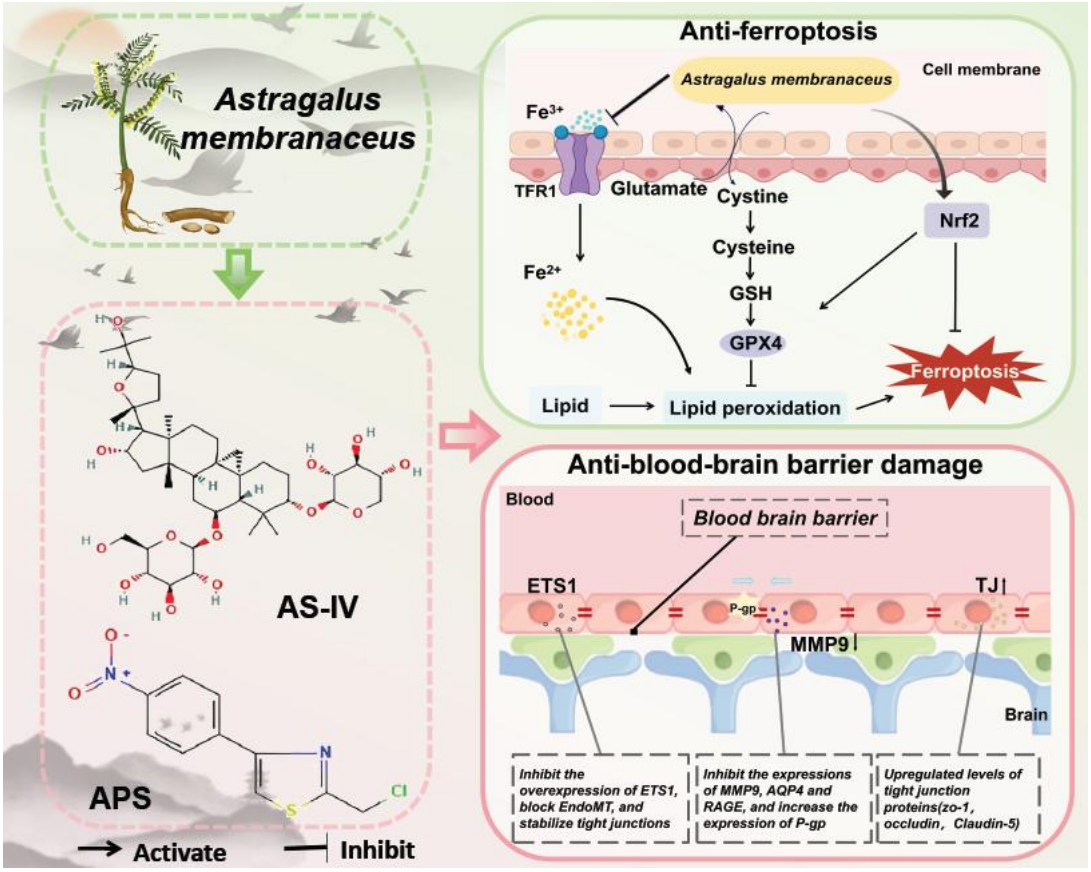

Figure 5. *Astragalus membranaceus* exerts anti-ferroptosis and anti-blood-brain barrier damage effects.

3.5.1. The Regulation of Gpx4 by Astragalus Membranaceus

GPX4 serves a distinctive role as a critical negative regulator of ferroptosis, primarily through its ability to convert lipid hydroperoxides into non-toxic lipid alcohols, thus interrupting the lipid peroxidation chain reaction. The proper functioning of GPX4 is essential for the regulation of ferroptosis. Inhibition of GPX4 may enhance cellular susceptibility to ferroptosis(Ma et al., 2022). TFA extracted from *Astragalus membranaceus* inhibited ferroptosis by up-regulating the SLC7A11/GPX-4 axis, as well as by increasing intracellular glutathione levels and GSH/GSSG ratio, in addition to which the researchers found that the use of the flavonoids extracted from *Astragalus membranaceus* as a dietary supplement might be beneficial for PD patients(Gao et al., 2024). Zhang et al. demonstrated that AS-IV enhanced the sensitivity of SLC7A11 and GPX4, both of which serve as indicators for evaluating ferroptosis. Additionally, AS-IV activated the Nrf2/HO-1 signaling pathway, thereby inhibiting ferroptosis and mitigating neuronal death in the MCAO model by modulating critical nodes within this pathway(Zhang et al., 2023). Interestingly, AS-IV administration in SAH similarly activates this pathway, inhibiting lipid peroxide accumulation and blocking the ferroptosis process in SAH(Liu et al., 2022). Researchers created selenium nanoparticles (TSIIA/TMP/APS@Se NPs)

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containing APS, Tan-shinoneIA, and tetramethylpyrazine, which effectively inhibited ferroptosis. These nanoparticles reversed the decline in neuronal numbers and GPX4 levels post-SCI and significantly reduced 4-hydroxynonenal, a lipid peroxidation marker, potentially improving functional recovery after SCI(Maiet al., 2025).

3.5.2. Astragalus Membranaceus Relies on Nadph to Function

The commonality of enzymes and metabolites important for resistance to lipid peroxidation during ferroptosis is the dependence on the key cellular reducing agent NADPH(Alveset al., 2025). In HT22 cells, AS modulators restored brain iron metabolism balance and stabilized lipid peroxidation by reducing NOX4 and activating the NOX4/Nrf2 signaling pathway. LPO homeostasis and inhibited ferrocyte apoptosis in SAMP8 mice, a mechanism that suggests the potential of AS modulators to inhibit ferroptosis and improve AD symptoms, making them a potential therapeutic candidate(Wang et al., 2025).

3.6. Anti-Blood-Brain Barrier Damage

BBB serves as the CNS's final defense against external threats, and its structural and functional stability is vital for preserving the neuronal environment (Figure 5). However, under pathological conditions such as AIS, AD, and MS, the BBB suffers from structural damage due to inflammatory cascades, oxidative stress imbalance, and metabolic reprogramming, with cascading increases in permeability, which exacerbates the formation of a neurotoxic microenvironment and triggers irreversible neuronal damage and dysfunction(Patabendige & Janigro, 2023).

3.6.1. The Regulation of Tight Junction Proteins by Active Ingredients of Astragalus Membranaceus

AST completely reversed LPS-induced BBB leakage and depressive behavior in a mouse model by down-regulating MMP-9 and up-regulating Claudin-5, suggesting that it may be an adjunctive neuroprotectant for the treatment of SAE(Cao et al., 2025). AS-IV increases TEER and reduces sodium fluorescein extravasation, and increases the expression of compact proteins such as zonula-1 and occludin, in LPS-stimulated bEnd.3 cells to protect the BBB(Li et al., 2018). Research has demonstrated that lanthanum, serving as a vascular permeability tracer during the intravenous administration of AS-IV, exclusively stains cerebral capillaries. This finding strongly suggests the BBB-protective properties of AS-IV, as it significantly inhibits the up-regulation of MMP-9 and AQP4 and mitigates cerebral vasogenic edema(Li, Ma, Li, Qu, & Gao, 2013). CAG not only mitigated oligomeric Aβ 1-42-induced apoptosis in bEnd.3 cells and enhanced the expression of tight junction scaffolding proteins, but also facilitated the efflux of soluble Aβ across BBB by upregulating P-gp and downregulating RAGE expression(Huang & Yu, 2021). ISOI, a cyclic alkane glycoside derived from *Astragalus membranaceus*, not only restored the reduced levels of tight junction proteins in LPS-stimulated bEnd.3 cells but also reduced BBB permeability by activating Nrf2 signaling pathway(Li et al., 2018). The combined administration of *Astragalus membranaceus* and Chuanxiongzine diminishes hemorrhage and Evans blue dye extravasation in the brain tissue of I/R mice, while enhancing the expression of tight junction proteins, thereby ameliorating the ultrastructural disruption of the BBB(Cai et al., 2014).

3.6.2. The Regulation of Ets1 by Astragalus Membranaceus

The transcription factor ETS1 is the central switch that triggers the endothelial-mesenchymal transition EndoMT and then disrupts the BBB. APS shows potential application in MS prevention by inhibiting the overexpression of ETS1, blocking EndoMT, and stabilizing tight junctions(Lu et al., 2024).

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3.6.3. Astragalus Membranaceus Combats Bbb Through Other Means

Astragalus membranaceus injection activates the BDNF/TrkB/CREB pathway, improving BBB function and reducing sepsis-induced neurological deficits(Liuet al., 2022). Furthermore, Hou et al. identified that AS-IV effectively inhibits endoplasmic reticulum stress-mediated endothelial cell apoptosis, thereby protecting the BBB and reducing the cerebral infarct area in I/R rats(Hou, Liu, Wu, & Huang, 2020b).

4. Pharmacognosy of Astragalus Membranaceus

4.1. Safety

On November 9, 2023, *Astragalus membranaceus* was officially recognized as an edible Chinese medicinal substance by China's health authorities. It shows low toxicity with no reported clinical side effects. In a study by Yu's team, rats and beagles received RAE (APS and AS) for 90 days without significant toxicity, even at doses 70 and 35 times higher than the human dose, respectively.(Yu et al., 2007). Xie's team conducted three-month gavage experiments on rats using *Astragalus membranaceus*, noting no fatalities or toxicity, confirming its safety. They established a NOAEL of 8800 mg/kg/day, 50 times the human clinical dose, further verifying the formulation's safety.(Xie et al., 2016). In summary, *Astragalus membranaceus* and its main active components are safe at standard doses in both short- and long-term toxicity tests, showing no significant side effects. However, high doses or prolonged use may lead to toxicity, so caution is advised.

4.2. Application of Astragalus Membranaceus in the Field of Food and Medicine

4.2.1. Application of Astragalus Membranaceus in Formulated Preparations

Astragalus membranaceus has been used in treating CNS diseases since its inclusion in Buyang Huanwu Decoction, as noted in Wang Qingren's "Medical Forest Right and Wrong." Modern studies show this decoction enhances nerve function and prevents neuronal damage through a multi-target mechanism. It reduces oxidative stress by inhibiting ROS, lowering MDA and 8-OHdG, and boosting SOD and GSH-Px. It also restores mitochondrial function, stabilizes energy metabolism, activates the PKCε/Nrf2/HO-1 pathway, and enhances antioxidant gene expression, forming a protective loop. These effects collectively reduce cerebral I/R injury and support recovery, supporting *Astragalus membranaceus*'s use in treating IS-related qi deficiency and blood stasis.(Yin, Liu, Wang, & Gao, 2023).

4.2.2. Application of Astragalus Membranaceus in Health Foods

Astragalus membranaceus is now added to health foods like drinks, pastries, and porridges, supporting the "medicine and food" philosophy (Figure 6). Patents show its use in three categories: liquid, semi-liquid, and solid, all for easy consumption (Table 1). These foods can boost the immune system and affect intestinal microbiota, which influences both digestion and brain health through the gut-brain axis(Tang et al., 2025). Thus, consuming *Astragalus membranaceus*-infused health foods may indirectly benefit brain health.

Liquid Products

Soups are common in medicinal diets. For example, *Astragalus membranaceus* chicken soup, made with black-boned chicken and goji berries, boosts qi, nourishes blood, and improves sub-health issues like qi and blood deficiency and fatigue. It can also help with appetite loss in diseases like PD and act as a supportive therapy.

Semi-Liquid Products

Semi-liquid products, known for their unique texture and easy digestion, are ideal for patients with CNS diseases post-surgery or radiochemotherapy. *Astragalus membranaceus* porridge,

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combining *Astragalus membranaceus* for kidney and spleen health with Japonica rice for stomach benefits, helps alleviate symptoms like memory loss and joint pain in AD patients with spleen and kidney deficiencies.

Solid Products

Within the staple food category, *Astragalus membranaceus* health biscuits are not only effective in alleviating hunger but also contribute to the physical well-being of patients with CNS disorders, offering health-enhancing benefits.

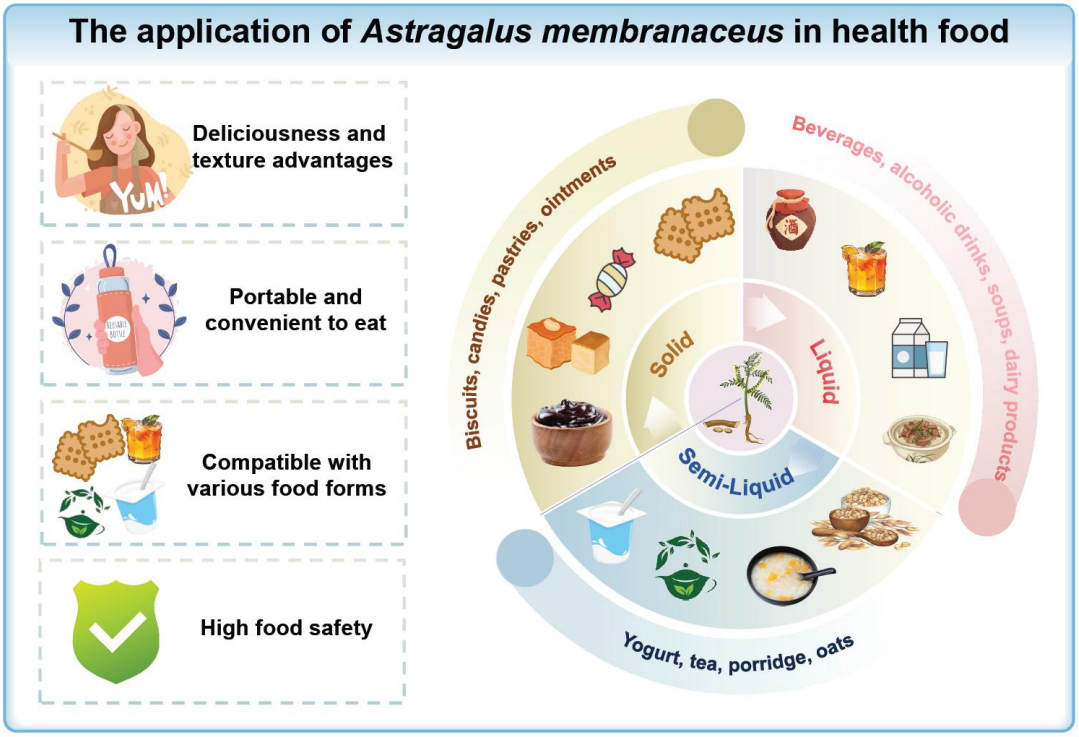

Figure 6. The application of *Astragalus membranaceus* in health food.

5. Summary

5.1. Neuroprotective Potential and Mechanisms of Astragalus Membranaceus Membranaceus in Cns Disorders

CNS diseases are marked by high levels of morbidity, mortality, and disability, posing a serious threat to human health. However, in current clinical practice, the efficacy of conventional drug therapy is not satisfactory and is accompanied by adverse effects. Natural Chinese medicines derived from herbs or plants have the advantages of biological activity, safety, and resource accessibility, and are becoming a valuable treasure trove for the development of new drugs. Currently, the high rate of disability in CNS diseases coexists with the problem of toxicity of existing drugs, making the search for low-toxicity, plant-derived neuroprotective agents an urgent need in the field of neurology. *Astragalus membranaceus* has been used in TCM for a long time(Liu, Li, Su, Liu, & Wen, 2025). Its signature active ingredients exert anti-neuroinflammation, anti-oxidative stress, anti-apoptosis, autophagy regulation, anti-ferroptosis, anti-BBB damage, etc., which deeply intervene in the core mechanism of CNS disease. Ferroptosis, a recently identified form of programmed cell death, has garnered considerable attention in the context of CNS diseases in recent years. Contemporary research suggests that its principal mechanisms involve signaling pathways such as GPX4, NOX4, and Nrf2. *Astragalus membranaceus* and its active constituents modulate ferroptosis through several mechanisms: they activate the Nrf2/HO-1 pathway, upregulate GPX4 expression, and enhance antioxidant capacity; they also inhibit NOX4 activity, reduce ROS generation, and stabilize lipid

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peroxidation balance. These effects have been substantiated in various CNS disease models, demonstrating notable neuroprotective properties. As previously discussed, the recent study revealed that *Astragalus membranaceus* exhibits significant neuroprotective effects against a range of CNS diseases through a synergistic mechanism characterized by a "multi-component-multi-target-multi-pathway" model, as demonstrated in both in vivo and in vitro models. Notably, preclinical studies consistently demonstrate that *Astragalus membranaceus* is free from both acute and long-term toxicity, ensuring high safety, and it is listed in the 'medicine and food' catalog(Feng et al., 2025). In recent years, the idea of "medicinal food" is shifting *Astragalus membranaceus* from "adjuvant treatment" to a focus on "early prevention and functional rehabilitation," offering a new strategy for precise intervention in CNS diseases.

5.2. The Limitations Faced in the Clinical Application and Promotion of Astragalus Membranaceus

Though the neuroprotective effects of *Astragalus membranaceus* in CNS diseases have been widely validated, its promotion in clinical practice still faces multiple limitations:

(1) The pathways and targets still need to be clarified. Existing studies focus on a single signaling axis (e.g., PI3K/AKT, Nrf2), and there is a lack of systematic analysis of the whole target network of *Astragalus membranaceus* in neuron-glia-vascular unit using a multi-omics integration strategy, which makes it difficult to translate the synergistic advantage of "multi-component-multi-target" into quantifiable biomarkers and precise intervention programs.

(2) The drug combination does not work. The role of the drug combination is unclear. When *Astragalus membranaceus* is used in combination with other drugs, it may affect the efficacy or increase the risk of adverse reactions, which still needs to be proved by clinical studies.

(3) Lack of clinical evidence. At present, most of the domestic and international studies on *Astragalus membranaceus* treatment of CNS diseases are cellular and animal experiments, lacking large-sample, multicenter, randomized controlled clinical data; in addition, the dose-exposure relationship of *Astragalus membranaceus* in various types of animal models and the effect of the route of administration on the bioavailability are still lacking systematic elucidation; whether long-term use of the drug induces tolerance, or leads to dry mouth, constipation, and other adverse effects, has not been seen in a definitive conclusion.

As a result, in order to successfully transition *Astragalus membranaceus* from the research laboratory setting into practical clinical use, it is essential that we gain a more detailed understanding of its underlying mechanisms of action. This involves conducting thorough scientific investigations to uncover exactly how *Astragalus membranaceus* functions within the biological systems. Additionally, it is crucial to refine and optimize the dosage protocols to ensure that the therapeutic benefits are maximized while minimizing any potential side effects. This optimization process should be based on comprehensive pharmacokinetic and pharmacodynamic studies. Furthermore, conducting high-quality, rigorous clinical trials is imperative to establish the safety and efficacy of *Astragalus membranaceus* in various patient populations. These trials should be designed with robust methodologies, including randomized controlled trials, to generate reliable and statistically significant data. Only through these concerted efforts can we hope to validate the clinical utility of *Astragalus membranaceus* and pave the way for its integration into standard medical practice.

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Abbreviations

TCM	traditional Chinese medicine
CNS	Central Nervous System
PD	Parkinson's disease
AS-IV	Astragaloside IV
APS	*Astragalus membranaceus* polysaccharides
CAG	Cycloastragenol
SCI	spinal cord injury
AD	Alzheimer's disease
TBI	traumatic brain injury
CI	cerebral infarction
NF-κB	Nuclear factor-κB
NLRP3	NOD-like receptor thermal protein domain associated protein 3
PPARγ	peroxisome proliferator-activated receptor γ
RRS	repeated restraint stress
LPS	Lipopolysaccharides
ROS	reactive oxygen species
RNS	reactive nitrogen species
SOD	superoxide dismutase
GSH-Px	glutathione peroxidase
NOX2/4	NADPH oxidase 2/4
T-AOC	total antioxidant capacity
AIS	Acute Ischemic Stroke
CA	Calycosin
PTZ	pentylenetetrazole
Rg1	Panax ginseng's
FMN	Formononetin
HGWD	Huangqi Guizhi WuWu Tang
JNK	c-Jun N-terminal kinase
p-ERK	phosphorylated extracellular signal-regulated kinase
CIRI	cerebral ischemia-reperfusion injury
CaSR	calcium-sensitive receptor
AMPK	Adenosine activated protein kinase
I/R	ischemia/reperfusion
OGD/R	oxygen-glucose deprivation/reoxygenation
TON	traumatic optic neuropathy
GPX4	Glutathione peroxidase 4
TFA	Total flavonoids
SAH	subarachnoid hemorrhage
NOX4	NADPH oxidase 4
LPO	Peroxidation
BBB	blood-brain barrier
MS	multiple sclerosis
SAE	sepsis-associated encephalopathy
P-gp	P-glycoprotein
RAGE	receptor for advanced glycation end-products
ISOI	Isoastragaloside I

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