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The Role of Astragalus Polysaccharides in Alzheimer's Disease: A Pharmacokinetic Review and Its Implications for the Peripheral-Cerebral Axis

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Abstract. Alzheimer's disease (AD) is a progressive neurodegenerative disorder in which cognitive decline is closely associated with amyloid-β deposition, tau pathology and persistent neuroinflammation. Astragalus polysaccharides (APS), one of the major bioactive fractions of Astragalus, have attracted attention because of their antioxidant, anti-inflammatory and immunomodulatory activities. Unlike small-molecule neuroprotective agents, however, APS are macromolecular polysaccharides with limited intestinal permeability and low brain exposure, making their mode of action difficult to explain by direct central nervous system penetration alone. This review summarises the reported pharmacological effects of APS relevant to AD and re-examines the available pharmacokinetic evidence from the perspective of absorption, distribution, metabolism and excretion. Current data suggest that APS are mainly retained in peripheral tissues rich in mononuclear phagocytes, particularly the spleen, liver and kidney, whereas brain exposure is low. After oral administration, APS may also be extensively degraded by gut microbiota into smaller oligosaccharide fragments. These findings support a working hypothesis that APS may influence AD pathology partly through peripheral immune regulation, gut microbiota remodelling and metabolite-mediated signalling rather than through direct accumulation in the brain. This peripheral–cerebral axis framework may help guide future mechanistic studies, formulation optimisation and dosing strategy design.

Keywords: Astragalus polysaccharides, Alzheimer's disease, pharmacokinetics, gut–brain axis, peripheral–cerebral axis, review

1. Introduction

Alzheimer's disease (AD) is a chronic neurodegenerative disorder marked by gradual impairment of memory, reasoning and daily functioning. The disease usually begins insidiously and progresses over years, imposing a substantial burden on patients, families and healthcare systems. According to the World Health Organization, approximately 55 million people worldwide live with dementia, and AD accounts for an estimated 60–70% of these cases.

Although considerable progress has been made in describing amyloid-β (Aβ), tau pathology, synaptic dysfunction and neuroinflammation, the pathogenesis of AD remains incompletely

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understood. Current therapeutic options are still limited, and many interventions mainly aim to relieve symptoms or slow progression rather than reverse the underlying disease process [1]. This situation has encouraged interest in multi-component and multi-target interventions, including compounds derived from traditional Chinese medicine.

Astragalus, known as Huangqi in Chinese medicine, has been widely studied in the context of immune regulation, inflammation and metabolic disorders. Its main bioactive constituents include saponins, flavonoids and polysaccharides. Among these, Astragalus polysaccharides (APS) have been repeatedly reported to show broad pharmacological activity with relatively low toxicity [2]. Nevertheless, a key question remains unresolved: if APS have poor oral absorption and limited brain exposure, how can they produce neuroprotective effects in AD-related models?

To address this question, this review focuses on the pharmacokinetic characteristics of APS and their mechanistic implications. Rather than treating APS simply as a central neuroprotective agent, the review considers whether APS may act through peripheral immune organs, gut microbiota and circulating inflammatory or metabolic signals. This perspective provides a more cautious and pharmacokinetically plausible explanation for the reported effects of APS in AD.

2. Alzheimer's disease

AD is characterised by progressive structural and functional damage in the brain. Clinically, it is associated with persistent cognitive decline and behavioural changes, with prevalence increasing markedly with age. AD is often classified into early-onset and late-onset forms, but both involve complex interactions among genetic, metabolic, inflammatory and environmental factors.

The two best-known pathological features of AD are extracellular Aβ plaques and intracellular neurofibrillary tangles (NFTs) formed by hyperphosphorylated tau. These lesions should not be viewed as isolated events. Increasing evidence suggests that Aβ accumulation, tau pathology and neuroinflammation interact with one another and form a self-reinforcing pathological loop [1].

Aβ is generated through sequential cleavage of amyloid precursor protein by β- and γ-secretases. When Aβ accumulates as soluble oligomers or fibrils, it can impair synaptic transmission, disturb calcium homeostasis and contribute to neuronal injury. In parallel, Aβ oligomers and damage-associated signals released from stressed neurons activate microglia. Activated microglia may then promote assembly of inflammatory complexes such as the NLRP3 inflammasome and increase the release of IL-1β and IL-18 [3]. These inflammatory mediators can aggravate synaptic loss and may further promote Aβ production and tau phosphorylation.

Tau pathology adds another layer to this process. Hyperphosphorylated tau detaches from microtubules, aggregates into paired helical filaments and eventually forms NFTs in neuronal cell bodies and axons. This disrupts cytoskeletal stability and axonal transport, thereby accelerating neuronal degeneration. Taken together, Aβ deposition, tau pathology and chronic neuroinflammation constitute a central pathological network in AD and provide a rationale for exploring anti-inflammatory and immunomodulatory interventions.

3. Astragalus polysaccharides

The medicinal part of Astragalus is the dried root of Astragalus membranaceus (Fisch.) Bge. var. mongholicus (Bge.) Hsiao or Astragalus membranaceus (Fisch.) Bge. [4]. Its major active constituents include astragalosides, flavonoids and polysaccharides. APS, as one of the main water-soluble components, have been associated with immunomodulatory, antioxidant, anti-inflammatory and antiviral activities.

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Early structural studies showed that Astragalus-derived polysaccharides are not a single uniform compound. Tomoda et al. [5] isolated a reticuloendothelial system-activating glycan with a molecular weight of approximately 6.0×10^4, containing L-rhamnose and D-galacturonic acid residues in its main chain. Shan et al. [6] further reported that APS isolated from Astragalus membranaceus roots contained rhamnose, arabinose, xylose, mannose, galactose and glucose. These structural differences are important, because molecular weight, branching pattern and monosaccharide composition may all influence biological activity and pharmacokinetic behaviour.

In the context of AD, the reported pharmacological effects of APS can be grouped into four main categories: antioxidant activity, anti-inflammatory effects, neuroprotection and immunomodulation. The following subsections summarise these effects with attention to the strength and boundary of the available evidence.

3.1. Antioxidant activity

Oxidative stress is closely linked to mitochondrial dysfunction, synaptic injury and neuronal loss in AD. APS may reduce oxidative injury through regulation of endogenous antioxidant pathways. In an H_2O_2-induced PC12 cell injury model, Liu et al. [7] found that APS increased the expression of antioxidant-related proteins, including HO-1, TrxR1 and NQO1, through activation of the Klotho-mediated Nrf2 pathway. This was accompanied by reduced reactive oxygen species (ROS) accumulation and decreased apoptosis. These findings indicate that APS may have antioxidant potential in neuronal injury models, although further validation in AD-specific in vivo systems is still needed.

3.2. Anti-inflammatory effects

Chronic neuroinflammation is now regarded as an important contributor to AD progression. Shi et al. [8] reported that APS can inhibit NLRP3 inflammasome activation in microglia and reduce the release of IL-1β and IL-18. In AD-related animal models, APS treatment was associated with decreased astrocyte proliferation and microglial activation around amyloid plaques. Behavioural data from the Morris water maze further suggested improved learning and spatial memory, as shown by increased platform crossings and shortened escape latency. These results support an anti-inflammatory role of APS, but they should be interpreted as model-based evidence rather than direct clinical proof.

3.3. Neuroprotective effects

The neuroprotective effects of APS have been examined in several experimental systems. Shi et al. [8] summarised evidence that APS may reduce Aβ deposition and improve cognitive performance through pathways such as JAK/STAT, Toll and IMD signalling. Li et al. [9] provided additional support using a Drosophila melanogaster AD model, in which APS delayed Aβ42-related phenotypes, extended lifespan and increased activity levels. APS has also been linked to improvement in insulin resistance, blood glucose regulation, intestinal barrier function and sleep-related abnormalities. These observations suggest that APS may act not only on neuronal cells but also on systemic pathological processes that are relevant to neurodegeneration.

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3.4. Immunomodulatory effects

Microglia are innate immune cells of the central nervous system and are highly responsive to Aβ, tau aggregates and other damage-associated signals. Persistent activation of microglia can shift them toward a pro-inflammatory phenotype, leading to cytokine release, synaptic damage and neuronal injury. Previous studies indicate that APS may suppress excessive microglial activation and promote a transition from the pro-inflammatory M1 phenotype toward the anti-inflammatory M2 phenotype [10]. In addition, APS has been reported to inhibit abnormal T-cell proliferation through the PD-1/PD-L1 pathway in a multiple sclerosis model, suggesting that its immunomodulatory effects may extend beyond AD-specific settings. This broader immunological activity is relevant when considering APS as a peripheral regulator rather than a compound acting only inside the brain.

4. Pharmacokinetic analysis

4.1. Absorption

The absorption profile of APS is strongly shaped by its macromolecular structure. Wang et al. [11] administered a single intravenous dose of IR783-labelled APS (APS-IR783, 30 $mg \cdot kg^{-1}$) to mice and found that plasma concentration peaked rapidly at 0.67 h, with a Cmax of 1599.29 $mg \cdot L^{-1}$. The elimination half-life reached 30.23 h, indicating slow systemic clearance after APS entered the circulation.The pharmacokinetic parameters reported by Wang et al. [11] are presented in Table 1. However, because this experiment did not include an oral APS control group, it cannot be used alone to estimate oral bioavailability.

For oral administration, available evidence suggests that APS have very low permeability because of their high molecular weight, high water solubility and poor ability to cross the intestinal epithelium [12]. Zhang et al. [12] proposed that APS may be hydrolysed by microbiota in the ileocecal region into oligosaccharides or monosaccharides before partial reabsorption. This implies that the intestine is not merely an absorption barrier but also a major site where APS are transformed into smaller, potentially active fragments.

Indirect evidence for enterohepatic circulation has also been reported. In the intravenous model, Wang et al. [11] observed a second plasma concentration peak at approximately 6 h, which coincided with increased signal in colonic tissue. This pattern suggests, but does not prove, that APS or related fragments may be excreted into the intestine through bile and then partially reabsorbed.

Table 1. Plasma pharmacokinetic parameters of APS-IR783 in mice (x±s, n=6)

parameter	value
Tmax (h)	0.67 ± 0.26
Cmax ($mg \cdot L^{-1}$)	1 599.29 ± 159.30
$T_{1/2}\alpha$ (h)	2.29 ± 3.06
T1/2β (h)	30.23 ± 19.98
AUC0-t ($mg \cdot h \cdot L^{-1}$)	23,398.91 ± 2,907.03
AUC0-∞ ($mg \cdot h \cdot L^{-1}$)	27,710.55 ± 3,506.55
MRT0–∞ (h)	34.38 ± 12.59
CL ($L \cdot h^{-1} \cdot kg^{-1}$)	0.001
Vz ($L \cdot kg^{-1}$)	0.042 ± 0.017

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4.2. Distribution

After intravenous injection, APS rapidly leave the plasma and accumulate mainly in organs rich in mononuclear phagocytes. The tissue-specific AUC values (see Table 2; data from Wang et al. [11]) revealed that the spleen, liver, and kidneys were the principal sites of APS accumulation.In the 72-h dynamic tissue distribution study by Wang et al. [11], the combined exposure of the spleen, liver, kidney, lung and heart accounted for 87.54% of total systemic tissue exposure. This distribution pattern suggests that uptake by the mononuclear phagocyte system and renal handling are major determinants of APS disposition.

Brain exposure was detectable but low. The reported brain AUC was 1498.51 $mg \cdot h \cdot L^{-1}$, accounting for only 1.54% of total tissue exposure. This signal may reflect low-level passive diffusion, intravascular retention or partial passage of labelled fragments. Because brain capillary depletion or intact-polysaccharide verification was not performed, the available data do not yet confirm that the parent APS molecule crosses the blood–brain barrier in meaningful amounts.

The apparent volume of distribution was also much lower than total body fluid volume, which is consistent with restricted diffusion of a large hydrophilic macromolecule. These findings favour the interpretation that APS function primarily as peripheral immunometabolic regulators. If direct central delivery is required, additional formulation strategies to enhance blood–brain barrier transport would probably be necessary.

Table 2. Tissue exposure ratios in mice following a single intravenous injection of 30 $mg \cdot kg^{-1}$ APS-IR783 (x±s, n=6)

tissue	$AUC_{0-\infty}$ ($mg \cdot h \cdot L^{-1}$)	exposure ratio (%)
spleen	22,734.99 ± 4,312.36	23.39
liver	20,376.27 ± 2,519.60	20.96
kidney	19,671.88 ± 2,280.32	20.24
lung	14,807.88 ± 1,482.60	15.24
heart	7,492.64 ± 2,549.40	7.71
small intestine	3,596.08 ± 492.20	3.70
muscle	3,163.65 ± 869.77	3.26
large intestine	2,534.06 ± 425.96	2.61
brain	1,498.51 ± 689.87	1.54
stomach	1,317.40 ± 286.96	1.36

4.3. Metabolism

Current pharmacokinetic studies have mainly traced fluorescence signals from IR783-labelled APS. This approach is useful for describing overall distribution, but it cannot distinguish intact polysaccharides from degraded fragments. As a result, the metabolic fate of APS remains only partly characterised.

Wang et al. [11] speculated that macromolecular APS may be taken up by macrophages in the liver and spleen and then gradually hydrolysed by lysosomal glycosidases into smaller fragments. More direct evidence for gut microbial metabolism was provided by Zhang et al. [12], who reported that after anaerobic incubation with rat faeces for 24 h, approximately 80% of high-molecular-weight APS was degraded into oligosaccharide fragments smaller than 3 kDa. Kou et al. [13] also isolated an acidic Astragalus polysaccharide, AMP-0.2A, and showed that its backbone contained

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repeating α-(1,2)-Rha-α-(1,4)-GalA units, with smaller structural units retaining immunomodulatory activity.

These findings suggest two possible metabolic routes. After intravenous administration, APS may be processed mainly within the liver and spleen through macrophage uptake and lysosomal hydrolysis. After oral administration, APS may first be cleaved by intestinal microbiota and then partly absorbed as oligosaccharides or other low-molecular-weight fragments. This distinction is important because the biologically active species after oral dosing may not be the original high-molecular-weight polysaccharide.

4.4. Excretion

APS show slow elimination after systemic exposure. In mice receiving intravenous APS-IR783 at 30 $mg \cdot kg^{-1}$, the apparent clearance was only 0.001 $L \cdot h^{-1} \cdot kg^{-1}$ and the terminal half-life was approximately 30 h [11]. These values indicate that the body lacks a rapid clearance pathway for intact macromolecular polysaccharides.

The exact excretion routes are still not fully resolved. One plausible pathway is uptake by mononuclear phagocytes, slow lysosomal degradation into smaller fragments, and subsequent elimination through respiratory, urinary or biliary routes. Isotope-tracing data provide partial support for respiratory elimination: after oral administration of 14C-labelled APS to rats, 14CO2 exhaled within 72 h accounted for 42% of the administered dose. However, total radioactivity recovery and the proportions of intact polysaccharide or oligosaccharide fragments in urine and faeces remain unclear. Further studies combining isotope tracing with LC–MS or other structural methods are therefore needed.

4.5. Implications for the peripheral-cerebral axis

The pharmacokinetic profile of APS makes a direct brain-accumulation mechanism unlikely to be the only explanation for its reported anti-AD effects. Brain exposure accounts for only a small fraction of total tissue exposure, and there is still no direct evidence that intact APS crosses the blood–brain barrier in substantial amounts. By contrast, APS are preferentially distributed to peripheral immune organs and can be transformed by gut microbiota into smaller fragments. These features point toward an indirect peripheral–cerebral mechanism.

At the peripheral immune level, APS have been reported to reduce inflammatory mediators such as TNF-α, IL-6, IL-1β and related cytokines in several experimental contexts [14]. This is relevant to AD because peripheral inflammation can influence central immune activity, especially when blood–brain barrier integrity is compromised. By lowering systemic inflammatory tone, APS may reduce the inflammatory signals that reach or affect the central nervous system.

At the intestinal level, oral APS may reshape the gut microbiota and increase the production of short-chain fatty acids. Wang et al. [15] reported that a 4-week APS intervention alleviated cognitive impairment in a triple-transgenic AD mouse model by increasing Akkermansia, reducing Alistipes, improving intestinal barrier integrity, and reducing neuroinflammation, Aβ deposition and tau pathology. Although this evidence is still preclinical, it provides a concrete link between APS, gut microbiota and AD-related brain pathology.

At the metabolic level, APS have also been associated with improved fasting blood glucose, reduced insulin resistance and lower hepatic inflammatory cytokine expression in type 2 diabetic rats [14]. Since metabolic dysfunction and low-grade systemic inflammation are increasingly

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recognised as contributors to AD progression, these peripheral metabolic effects may be another route by which APS indirectly modulate neurodegenerative processes.

Taken together, the available evidence supports a chain-like model: APS are retained in peripheral immune tissues or degraded by gut microbiota; this leads to changes in cytokine profiles, microbial composition and circulating metabolites; these peripheral signals then influence microglial activation, neuroinflammation and AD-related pathology. This model is more consistent with the pharmacokinetic data than a simple assumption of direct brain penetration.

5. Conclusion

This review examined the pharmacological and pharmacokinetic evidence for APS in relation to AD. APS have been reported to show antioxidant, anti-inflammatory, neuroprotective and immunomodulatory effects in cellular and animal models. However, their pharmacokinetic properties indicate that they are mainly distributed in peripheral organs rich in mononuclear phagocytes, while brain exposure remains very limited. After oral administration, APS are likely to be extensively degraded by gut microbiota, and their active forms may include smaller oligosaccharide fragments rather than the intact parent polysaccharide.

Therefore, the potential anti-AD effects of APS should be interpreted through a peripheral–cerebral axis framework. APS may influence AD-related pathology by regulating peripheral inflammation, gut microbiota, intestinal barrier function and systemic metabolic status. This interpretation does not exclude direct central effects, but it places them within a more cautious pharmacokinetic context.

6. Outlook

Several issues deserve priority in future research. First, the gut–brain and peripheral immune mechanisms need direct experimental verification. Fecal microbiota transplantation, antibiotic intervention, adoptive transfer of peripheral immune cells and blood–brain barrier assessment could help determine whether the neuroprotective effects of APS are mediated by microbiota remodelling, immune regulation or metabolite signalling.

Second, the active species of APS after administration should be clarified. Fluorescence imaging alone cannot distinguish intact APS from labelled fragments. Future studies should combine isotope tracing, LC–MS-based structural analysis and molecular-weight fractionation to identify which fragments enter circulation and which components are responsible for biological activity.

Third, computational approaches may be useful, but they should be used as hypothesis-generating tools rather than substitutes for experimental validation. Network pharmacology, molecular docking and machine-learning integration of metagenomic, metabolomic and transcriptomic data could help identify candidate targets such as NLRP3, Nrf2 and JAK/STAT-related pathways. These predictions need to be tested in well-designed cellular, animal and eventually clinical studies.

Finally, long-term safety and combination strategies should be evaluated before clinical translation. APS may have potential as an adjunctive intervention, particularly in AD patients with inflammation, metabolic dysfunction or gut microbiota disturbance. Whether APS can synergise with cholinesterase inhibitors, memantine or emerging disease-modifying therapies remains an important question for future work.

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