International Journal of General Medicine

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

The Bidirectional Mechanism of Uric Acid Levels on Alzheimer's Disease: A Narrative Review

Jingyi Zhao, Xinwei Wang, Baolong Li

Drug Safety Evaluation Center of Heilongjiang University of Chinese Medicine, Harbin, Heilongjiang, People's Republic of China

Correspondence: Baolong Li, Drug Safety Evaluation Center of Heilongjiang University of Chinese Medicine, 24 Heping Road, Xiangfang District, Harbin City, Heilongjiang Province, 150006, People's Republic of China, Tel +86 13804519725, Email lbl73@163.com

Abstract: Alzheimer's disease (AD) is a central nervous system disorder marked by the extracellular accumulation of β-amyloid (Aβ) plaques in the cerebral cortex and the intracellular aggregation of hyperphosphorylated tau protein, manifesting as progressive cognitive decline and neurodegeneration. The pathological mechanisms of AD are intricate, in clinical treatment, cholinesterase inhibitors have been widely used for many years as symptomatic therapy, alleviating symptoms by improving neurotransmitter levels, but they cannot halt disease progression. Anti-Aβ monoclonal antibodies belong to disease-modifying therapies, although they have achieved breakthrough advances in recent years, strict monitoring requirements must be followed. In recent years, numerous studies have revealed a "U-shaped" association between uric acid (UA) levels and AD risk, along with population heterogeneity. Furthermore, fluctuations in UA levels exert a "bidirectional effect" on AD. At physiological concentrations, UA may confer neuroprotective benefits through antioxidant activity, inhibition of neuroinflammation, preservation of the blood-brain barrier (BBB), regulation of autophagy, and promotion of the clearance of Aβ and tau proteins. Conversely, abnormal UA levels may accelerate AD progression by inducing oxidative stress, activating inflammatory responses, and compromising the BBB. We conducted a comprehensive literature review across multiple medical databases, including PubMed, Embase, Cochrane Library, Web of Science, Scopus, China National Knowledge Infrastructure (CNKI), and Wanfang Data. The selected articles underwent critical evaluation, summarization, and incorporation into this review to highlight research achievements in this domain. This narrative review summarizes current pharmacological treatments for AD and UA, encompassing traditional Chinese medicine (TCM) monomers, compounds, and Western medications. It also thoroughly explores and elucidates the complex mechanism underlying the "bidirectional effect" of UA levels and metabolic pathways on AD, offering insights and theoretical support for future AD drug development.

Plain Language Summary: In the handling of UA, humans, monkeys, and mice have embarked on three distinct evolutionary pathways, with uricase serving as a critical determinant. Mice and most other mammals possess this efficient metabolic tool, enabling effective UA decomposition and preventing accumulation. Although monkeys retain the uricase gene, its activity has significantly declined. Meanwhile, throughout millions of years of evolution, humans have completely lost functional uricase genes, rendering our species particularly susceptible to UA-related disorders. This seemingly regressive evolutionary path actually conceals survival advantages: in ancient environments, UA functioned as a potent antioxidant that protected against free radical damage, served as an energy reserve during food scarcity, and potentially facilitated brain development—thereby contributing crucially to the survival and reproduction of human ancestors. However, this evolutionary heritage has become a double-edged sword in modern times. Contemporary high-calorie diets and sedentary lifestyles have dramatically increased the risk of UA metabolic disorders, transforming this ancient survival advantage into a pressing health challenge requiring scientific management.

Keywords: serum uric acid, Alzheimer's disease, U-shaped association, neuroprotection, Neuroinflammation, blood-brain barrier

Introduction

Alzheimer's disease (AD) is a central nervous system disorder characterized by the extracellular accumulation of β-amyloid (Aβ) plaques in the cerebral cortex and the intracellular aggregation of hyperphosphorylated tau protein.[1] Its prominent clinical manifestations include progressive cognitive decline and neurodegenerative changes, accounting for 60–80% of all

Received: 14 September 2025
Accepted: 27 November 2025
Published: 16 December 2025

cases of dementia.[2] The onset of AD is modulated by global metabolic pathways and involves multiple intersecting biological cascades. Therefore, early diagnosis of individuals with AD and targeted intervention for individual disease progression are critical to delaying AD pathogenesis.

Uric acid (UA) is the final product of purine metabolism in the human body and functions as a natural antioxidant. Recent studies have revealed a "U-shaped" relationship between UA levels and the risk of AD, along with population heterogeneity, wherein different UA levels exert a "bidirectional effect" on AD.[3] Under physiological conditions (with blood UA levels ranging from 208 to 428 μmol/L in healthy individuals), UA may safeguard nerve cells and decelerate the pathological progression of AD through mechanisms such as mitigating oxidative stress (OS), suppressing neuroinflammation, and regulating Aβ metabolism.[4] Conversely, abnormal UA levels (concentrations exceeding 428 μmol/L or falling below 208 μmol/L in the blood) may intensify AD damage progression by inducing amino acid metabolism disorders, promoting UA crystal deposition, triggering neuroinflammation, and compromising the blood-brain barrier (BBB).[3,5] The optimal UA concentration range for this protective effect varies based on gender, age, and the presence of other influencing factors (including chronic kidney disease, obesity, metabolic syndromes like diabetes, or menopause). However, the overall core characteristic remains a "U-shaped" association characterized by "protection within the normal range and damage at both abnormal ends."

We performed a literature review across several medical databases, encompassing PubMed, Embase, Cochrane Library, Web of Science, Scopus, China National Knowledge Infrastructure (CNKI), and Wanfang Data. Search terms were related to AD, UA levels, neuroinflammation, neuroprotection, and U-shaped associations. We retrieved, collated, and synthesized relevant studies to present the research accomplishments in this domain. This narrative review outlines the correlation between UA levels, metabolic pathways, and the AD microenvironment, delves into the bidirectional mechanisms and pivotal targets of UA's effects on AD, and underscores the potential of UA levels as a biomarker for identifying individuals at high risk for AD and as a novel therapeutic target, albeit with uncertain predictive accuracy. Additionally, it summarizes the contemporary applications of traditional Chinese and Western medicine in treating UA and AD, offering clinicians innovative treatment strategies for regulating UA levels and preventing AD.[6]

Different UA Levels, Metabolic Pathways, and Microenvironmental Changes in AD

Physiological Metabolic Pathways of UA

UA is an effective endogenous antioxidant in plasma, primarily existing in the form of urate at physiological pH. The production and excretion of UA adhere to a strict dynamic balance, regulated by three core processes: synthesis – transport – excretion. This equilibrium depends on UA's biosynthesis, transport mechanisms, and its excretion through the kidneys and intestines.[7]

Purines are the primary source of UA synthesis in the body. Endogenous purines, accounting for approximately 80% of total purines, are derived from the breakdown of amino acids and nucleic acids within the body, while exogenous purines originate from dietary sources such as red meat (beef, lamb), seafood, legumes, and animal offal. The metabolic activity of endogenous purines is a key determinant of UA level fluctuations. Two critical enzymes in UA biosynthesis are adenosine deaminase (ADA) and xanthine oxidase (XOD): ADA catalyzes the conversion of adenosine to hypoxanthine, which is then oxidized by XOD to synthesize UA.[8] The kidneys are the main organs responsible for UA transport and excretion. Approximately 70% of UA is filtered through the glomeruli, with 90% of this amount subsequently reabsorbed by renal tubules. This process is regulated by multiple factors, including UA transporters such as URAT1, GLUT9, and OAT4/10 (which mediate reabsorption), and ABCG2, OAT1/3, MRP4, and NPT1/4 (which promote excretion).[9,10] The remaining UA is excreted through the intestines and biliary tract. Notably, the composition and function of gut microbiota significantly influence UA metabolism in the intestines. Studies indicate that certain probiotics (Bifidobacterium, Lactobacillus) can modulate gut microbial balance, enhance UA metabolism, and reduce systemic UA levels.[11]

U-Shaped Curves and Population Heterogeneity Associated with AD at Different UA Levels

There is a U-shaped curve relationship between different levels of UA and the population of AD patients. The shape of this curve is mainly closely related to factors such as UA levels, the age and gender of AD patients. The kidney serves as the primary organ for UA excretion, and chronic kidney disease results in decreased UA excretion due to a reduced glomerular filtration rate and impaired renal tubular function, thereby aggravating hyperuricemia (HUA). In addition, components of metabolic disorders, including abdominal obesity and insulin resistance, inhibit UA excretion and stimulate purine synthesis, leading to a heightened risk of HUA and exerting a certain influence on the onset of AD. Given that the analysis draws on diverse research populations, we cannot entirely rule out the potential impacts of chronic kidney disease, metabolic syndrome, and other related factors.

There are significant gender differences in serum UA levels: the normal range for males is 208–428 μmol/L, while that for premenopausal females is 149–357 μmol/L.[12] Notably, postmenopausal females experience a decrease in UA excretion due to reduced estrogen levels, leading to serum UA levels similar to those of males.[13] Within the normal physiological range, UA may exerts neuroprotective effects via its potent antioxidant properties. At this stage, brain inflammatory activity is negatively correlated with serum UA concentration, which may helps reduce the risk of AD onset; However, when UA concentration exceeds the physiological saturation threshold (≈420 μmol/L in males and ≈360 μmol/L in females), high UA levels promote OS and may induce UA crystal deposition, thereby increasing the risk of AD;[14] Meanwhile, low UA levels may weaken endogenous antioxidant and other defense functions, accelerate disease progression driven by OS, and are recognized as one of the risk factors for accelerated AD progression;[15] Kim et al's cross-sectional study on patients with neurodegenerative diseases (NDs) showed that among 840 patients with different types of NDs, serum UA levels were significantly lower than those in 839 healthy controls; it confirmed that in 111 patients with tauopathies (diseases characterized by tau protein aggregation, including AD), low serum UA levels were associated with disease progression and were also lower than those in 130 healthy controls;[16] Sholefield et alconducted case-control studies and meta-analyses, which also demonstrated that low UA is associated with an increased risk of Parkinson's disease and AD (a major type of dementia);[17] At the same time, Huang R et al found in patients with type 2 diabetes that UA was associated with cognitive function in a U-shape, with the optimal protective range being 238–357μmol/L; UA levels lower or higher than this range increased the risk of AD.[18]

It can be inferred that different levels of UA have a bidirectional effect in AD: physiological concentrations of UA are highly effective antioxidants that can clear free radicals and protect neurons; And pathological concentrations (>420 μ mol/L or<120 μ mol/L) may promote the development of AD by inducing OS, activating inflammatory responses, etc (Figure 1).[19]

The Bidirectional Regulation Mechanism of UA on AD

The pathophysiological mechanisms of AD are complex. Key contributing factors include OS-induced mitochondrial dysfunction, neuroinflammation mediated by the TLR4/NF-κB/NLRP3 inflammatory pathway, Aβ aggregation, tau protein hyperphosphorylation, and impaired BBB integrity. As one of the most abundant natural water-soluble antioxidants in human serum, UA can scavenge excessive free radicals in the body—including superoxide anions (O_2^-), hydroxyl radicals (·OH), and peroxynitrite anions ($ONOO^-$)—and accounts for approximately 50% of extracellular antioxidant capacity. Liu et al performed multiple regression analysis on 69 AD patients and 67 healthy controls, showing that UA exerts a bidirectional effect on OS: while physiological UA levels are protective, relatively high UA levels may promote AD progression.[20] Physiological serum UA levels play a critical antioxidant role in the body. Within the brain—where molecular access is restricted by the BBB—UA serves as a key endogenous antioxidant: it scavenges the excessive accumulation of reactive oxygen species (ROS), alleviates OS, protects neurons against OS-induced inflammatory stimuli, regulates Aβ aggregation and tau protein hyperphosphorylation, preserves BBB tight junction integrity, and slows AD progression. However, when serum UA levels are abnormal, high UA concentrations can form crystals that deposit in brain tissues, exacerbating AD by reversely regulating the aforementioned pathways (Figure 2).

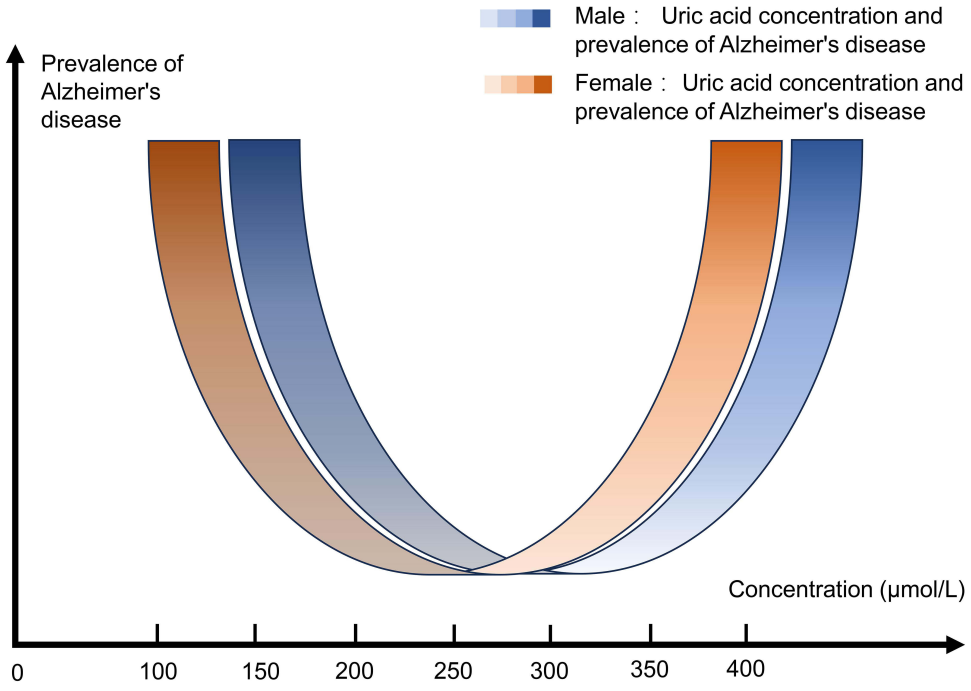

Figure 1 Trend chart of the association between uric acid concentration and Alzheimer.

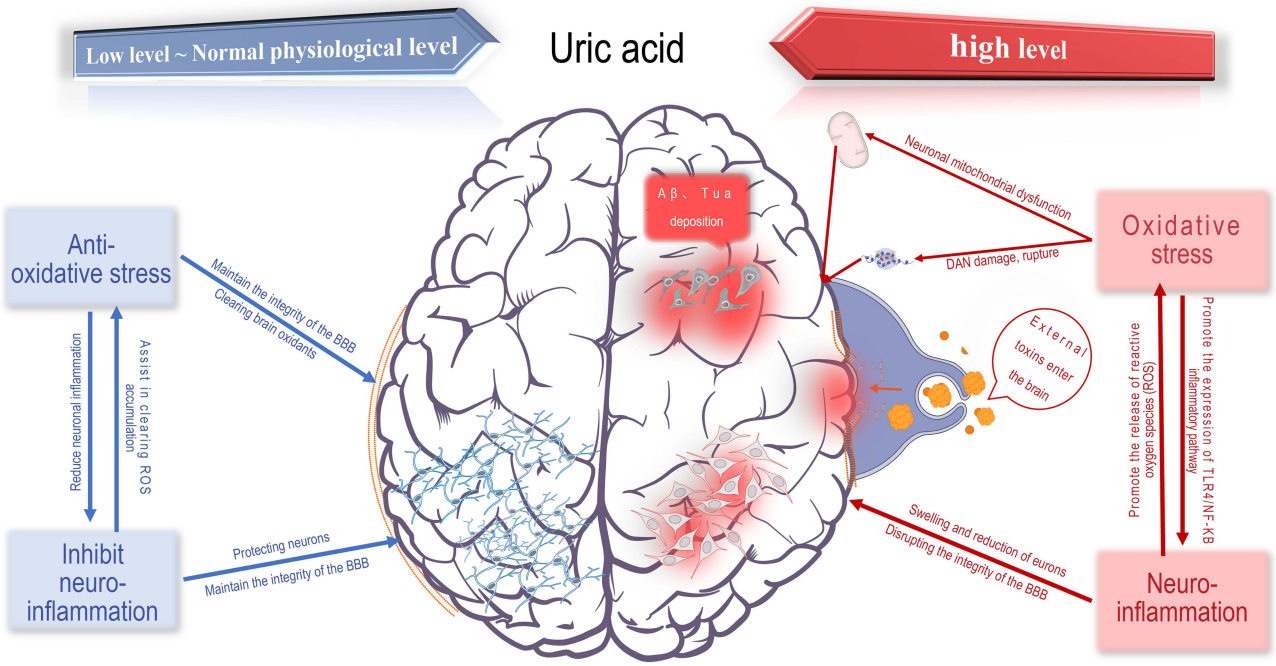

Figure 2 Two-way mechanism of action between uric acid level and Alzheimer's disease.

UA's Protection Mechanism Against AD

Antioxidant Stress: Resist ROS Burst and Protect Neuronal Mitochondrial Function

Aβ accumulation is the primary pathological hallmark of AD. Within this process, the hydrophobic domain of Aβ directly activates NADPH oxidase 2 localized on neuronal membranes, triggering a surge in O_2^- production. This, in turn, drives the explosive accumulation of ROS in AD-affected brain regions, activating the OS pathway, inducing

mitochondrial dysfunction, and ultimately exacerbating AD pathogenesis. Neuronal membranes are rich in polyunsaturated fatty acids and highly susceptible to ROS-induced damage. Following lipid peroxidation, severe OS is observed in the brains of AD patients—characterized by elevated levels of lipid peroxidation products malondialdehyde and protein oxidation products 8-hydroxyguanine.[21] In the central nervous system, UA acts as a potent scavenger of $ONOO^-$: it can terminate free radical chain reactions, neutralize $ONOO^-$ to reduce OS-mediated DNA damage, and thereby protect neurons from oxidative injury.[22] Aerqin et al observed in a cross-sectional study of patients with NDs that the strong association between serum UA and AD protection may be attributed to the inhibition of excessive OS.[23] Specifically, UA mitigates ROS accumulation and protects neurons against glutamate-induced toxicity by scavenging free radicals and chelating pro-oxidative metal ions. Meanwhile, Pinz et al found that UA can further alleviate OS-induced neuronal damage and improve cognitive function by inhibiting lipid peroxidation and attenuating neuroinflammatory responses.[24] Regardless of the specific downstream pathways, the antioxidant protective role of UA in AD is widely acknowledged, and this mechanism contributes to preventing AD pathogenesis.[25]

Anti-Inflammatory: Inhibit the Activation of TLR4/NF-κB and Other Pathways, Alleviate Neuronal Inflammation

The brain inflammatory microenvironment is a key driver of AD progression, and the activation and inflammatory responses of glial cells and neurons are recognized as key hallmarks of AD pathogenesis.[26] Among canonical inflammatory regulatory pathways implicated in multiple diseases, the TLR4/NF-κB signaling pathway exerts a critical regulatory role in AD. For instance, various Toll-like receptor (TLR) family molecules serve as primary upstream initiators of inflammation. Upon binding to cells, they activate the expression of target genes like nuclear factor kappa-B (NF-κB), triggering an inflammatory response. Thus, upstream inflammatory activators like the TLR family are key sites of UA regulation. Studies have revealed that high levels of UA within the range of 416–713 μmol/L, commonly observed in patients with severe renal insufficiency, can inhibit TLR signaling in monocytes, thereby impairing cytokine production and the migration of CD14+ monocytes in vitro.[27] Additionally, Ma et al discovered in cellular experiments that UA impairs β2 integrin activation and signaling, leading to reduced migration of neutrophils to inflammatory sites in vivo and alleviating inflammatory responses.[28] Wang et al found in a mouse model of middle cerebral artery occlusion/reperfusion that UA could inhibit TLR4/NF-κB signaling in microglia, suppress the release of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, and alleviate microglia damage.[29] In addition to the TLR4/NF-κB pathway, Gong et al discovered that UA could improve memory impairment and neuroinflammation in APP/PS1 transgenic mice, enhance brain adenosine monophosphate-activated protein kinase (AMPK) activation, reduce the activation of p38/MAPK and p65/NF-κB, and inhibit the degradation of amyloid precursor protein (APP) and amyloid precursor protein β-site cleavage-1, thereby affecting key cellular signaling pathways, preventing neuronal apoptosis, and improving cognitive impairment.[30]

Inhibition of Aβ and Tau Deposition: Regulating Autophagy Pathway and Reducing Erroneous Protein Deposition

The abnormal accumulation of Aβ and tau proteins is a primary driver of AD pathogenesis. Impaired autophagy in the brain—leading to defective clearance of misfolded proteins and subsequent pathological deposition—is recognized as one of the key mechanisms underlying AD development. Studies have demonstrated that modulating autophagic activity can retard AD progression.[31] Transcription factor EB (TFEB) is the primary transcriptional regulator of autophagy, which can enhance the expression of genes related to autophagosome formation, lysosomal function, and autophagy flux.[32] UA can regulate cellular autophagy function by increasing the expression level of TFEB in cells, promoting the metabolic processes of Aβ and tau proteins, and alleviating cognitive dysfunction in AD patients.[33] Qian et al further investigated this mechanism in two AD models: Aβ-induced AD model mice and APP23/PS45 double-transgenic AD model mice.[34] Their results showed that UA not only directly mitigates OS but also enhances TFEB's transcriptional regulation of autophagy-related genes by promoting TFEB nuclear translocation. This process stimulates microglial autophagy, accelerates Aβ clearance, and thereby exerts neuroprotective effects. Separately, Fang et al explored the role of UA in AD and found that UA ameliorates memory deficits and cognitive impairment in APP/PS1 transgenic mice by inducing mitophagy.[35] Specifically, mitophagy reduces levels of hyperphosphorylated tau protein and decreases the

expression of insoluble Aβ species (Aβ1-42 and Aβ1-40). Additionally, mitophagy enhances microglial phagocytosis of extracellular Aβ plaques, which in turn inhibits neuroinflammation and retards AD progression.

Protecting the Blood-Brain Barrier: Regulating KLF2/VEGF-A Axis and MMPs/TIMPs Balance

The BBB is a specialized barrier formed by continuous, tightly connected endothelial cells of cerebral microvessels. Its tight junctions strictly restrict the entry of blood-borne substances into the brain parenchyma, thereby maintaining central nervous system homeostasis. BBB structural impairment is recognized as one of the early pathological hallmarks of AD.[36] Neurons are highly susceptible to OS, and brain tissue exhibits high metabolic activity and abundant lipid content—rendering it prone to free radical generation. Notably, the BBB restricts the entry of most exogenous antioxidants into the brain, which underscores the importance of UA as a critical endogenous antioxidant within the CNS.[37] Krüppel-like factor 2 (KLF2) and vascular endothelial growth factor A (VEGF-A) exert complex synergistic and antagonistic effects in regulating BBB tight junctions. Specifically, KLF2 functions as the core transcription factor that regulates the expression of BBB tight junction proteins, thereby exerting a protective effect on BBB integrity; in contrast, VEGF-A typically exerts the opposite effect. Vila et al found that UA maintains the expression of tight junction proteins in the BBB by activating the KLF2/VEGF-A axis, reducing inflammatory cell infiltration.[38] Meanwhile, intravenous injection of UA in animal models can induce KLF2 expression, decrease VEGF-A levels, alleviate endothelial dysfunction in the brain, and improve the integrity of the BBB barrier. UA also reduces matrix metalloproteinase 9 expression and BBB basement membrane degradation by regulating the activity of tissue inhibitor of metalloproteinases (TIMPs), maintaining its integrity.[39] Laura et al emphasized in clinical trials that the combination of exogenous UA and the thrombolytic agent alteplase improves clinical outcomes in patients with ischemic stroke by inhibiting malondialdehyde production and matrix metalloproteinase 9 activation, exerting additional neuroprotective effects.[40] Cao et al found in patients with anti-N-methyl-D-aspartate receptor encephalitis that serum UA levels decreased, accompanied by a decrease in the BBB index, suggesting that low UA concentration is related to BBB integrity.[41]

The Damage Mechanism of UA on AD

Promoting Oxidative Stress: The Core Mechanism by Which UA Affects AD

During cerebral ischemia, brain tissue generates UA via neuronal XOD, concurrently with a surge in ROS production. This explosive accumulation of ROS activates the OS pathway, inducing neuronal injury and apoptosis via activation of pro-inflammatory signaling pathways in the brain, it also promotes BBB disruption, as well as Aβ and tau protein deposition.[26] Meanwhile, infiltrating inflammatory cells release various pro-oxidative and pro-inflammatory mediators that further amplify OS, creating a reciprocal amplification loop between neuroinflammation and OS—termed an "OS-inflammatory cascade"—which exacerbates AD progression.[42] et al al investigated this interplay in NDs and found that elevated UA (not physiological UA) inhibits AMPK activation, accelerates OS progression, upregulates the expression of pro-inflammatory mediators, and thereby exacerbates vascular dementia and other NDs.[43] Additionally, cognitive impairment driven by elevated UA is mediated by two key mechanisms: OS amplification and cerebral ischemic insults. As OS progresses, it induces vascular endothelial protein oxidation and vascular smooth muscle cell proliferation, leading to endothelial damage, BBB structural disruption, and the induction of lacunar cerebral infarcts—all of which contribute to cognitive impairment in affected patients. Thus, the exacerbation of OS directly perturbs these interconnected pathological pathways (neuronal injury, BBB damage, Aβ/tau deposition), creating a vicious cycle that collectively accelerates AD progression.

Inflammation promoting: UA deposition activates pathways such as TLR4/NF-κB, exacerbating neuronal inflammation

Low concentrations of UA (such as within the normal serum range) may exert antioxidant effects by scavenging ROS. However, when UA concentrations exceed the solubility limit (≈420 μmol/L in males and ≈360 μmol/L in females), UA forms crystals that deposit in tissues. HUA and UA crystals have been shown to activate microglia and astrocytes, subsequently activating the TLR4/NF-κB/NLRP3 signaling pathway and promoting the release of inflammatory factors such as TNF-α and IL-6, thereby triggering neuroinflammation and further accelerating the development of cognitive dysfunction.[44] UA deposition promotes the expression of NF-κB by activating TLR4, thereby increasing the production

of precursor IL-1β. Under hypoxic conditions, hypoxia-inducible factor 1αis activated, which catalyzes the conversion of pro-IL-1β into mature IL-1β. By binding to the IL-1β receptor, it reactivates the expression of NF-κB, forming a positive feedback loop. Ultimately, IL-1β triggers inflammatory reactions in the hippocampus and leads to the progression of cognitive dysfunction. Husejko et al found in a clinical comparative study between untreated and treated patients with HUA that, in the case of properly treated HUA, there was a weak negative correlation between UA levels and interleukin IL-1β levels, and no statistically significant correlation was found between UA levels and interleukin-6 levels.[4] However, in untreated patients with HUA, there was a statistically significant positive correlation between UA and the levels of interleukins IL-6 and IL-1β, suggesting that HUA has a potential impact on systemic inflammation. Meanwhile, research has shown that long-term HUA induces the development of cognitive impairment by triggering the release of OS, TNF-α, and the accumulation of Aβ. Tian et al found in the HUA rat maintenance model from the 6th to the 48th week that the accumulation of OS, TNF-α, and Aβ induced cognitive impairment and increased the risk of AD.[45] Xiao et al found in their study that high concentrations of UA enhance ROS generation, stimulate OS reactions, such as increased XOD activity, leading to lipid peroxidation and DNA damage, further exacerbating inflammation.[46] Therefore, HUA and UA crystal deposition are considered as high-risk factors for AD.[47]

Disrupting BBB Permeability: Promoting Inflammation Development and Harmful Substances Entering the Brain

The disruption of BBB integrity can lead to the entry of inflammatory factors such as TNF-α and damaging substances like Aβ into the brain, exacerbating the progression of AD. High UA-induced BBB cerebrovascular endothelial dysfunction can hinder Aβ clearance, while simultaneously damaging vascular endothelial cells and disrupting BBB junctional function.[48] UA can pass through the BBB and act as a potent inflammatory stimulus, thereby resulting in TLR4/NF-κB pathway activation as well as the accumulation of gliosis in the hippocampus, thereby inducing cognitive dysfunction.[49] Long-term hippocampal inflammation exacerbates the formation and progression of cognitive impairment by inhibiting the regeneration of neural stem cells and increasing neuronal apoptosis.[49,50] In their study on immunoproteasomes and NDs, Chen et al found that compared to rats in the control group, high levels of UA were accompanied by elevated OS levels, leading to the reactivation of astrocytes and microglia, increased expression of IL-6 and TNF-α, and downregulation of tight junction protein expression in the BBB, resulting in increased leakage, enhanced Aβ deposition, and aggravated NDs.[51] Therefore, the loss of BBB integrity is one of the causes of AD.

Application of Traditional Chinese and Western Medicine in the Treatment of UA and AD

Through sorting out the existing drugs for the treatment of UA and ad, several drug lists have been formulated for some drugs, including drugs in the experimental phase, clinical trial phase and approved by FDA and nmpa, which are sorted out in Tables 1–3.

Traditional Chinese and Western Medicine Treatment of UA Drugs

Although there are various drugs currently available to regulate UA levels, they mostly target XOD and superoxide dismutase (SOD) for their effects. Traditional Chinese medicine (TCM) mainly inhibits UA production, promotes excretion, reduces OS, anti-inflammatory and other multi-target combinations, while Western medicine mainly targets XOD and SOD for treatment. Table 1 summarizes the existing drug research on regulating UA in both Chinese and Western medicine.

Chinese and Western Medicine Drugs for Treating AD

At present, the development of AD delaying drugs is relatively limited, and the treatment drugs for AD mainly focus on targeted clearance of Aβ plaques and Tau protein. The mechanism is mainly based on Western single target therapy and multi-point regulation of TCM and compound formulas. Tables 2 and 3 summarize the existing drug research on regulating AD in both traditional Chinese and Western medicine.

Table 1 Medications for the Treatment of UA in Traditional Chinese and Western Medicine

Drug Category	Drug Name	Target Spot	Partial Mechanism of Action	Regulatory Status	Citation
Traditional Chinese medicine monomer	Luteolin	XOD, SOD	In the study of gouty arthritis model, luteolin can reduce the expression of XOD and SOD, inhibit inflammation, reduce UA, and alleviate gouty arthritis	Research progress	[52]
	Total glycosides of Semen Plantaginis	XOD	In the study of Hua rat model, it was found that the total glycosides of Semen Plantaginis can reduce the expression of XOD in serum and liver tissue, and combine with the regulation of intestinal flora to reduce UA level and slow down Hua	Research progress	[53]
Traditional Chinese medicine compound	Wuling capsule	XOD	In the study of rat model of Hua, it was found that Wuling capsule could reduce the UA level and slow down Hua by reducing the content of UA, XOD, etc. in rat serum	NMPA approval	[54]
	Simiao pill	Uric acid transporter (ABCG2)	In the study of intestinal barrier function and intestinal flora of Hua, it was found that ABCG2 was upregulated in Simiao pill treatment group, which promoted UA transport and excretion and slowed down Hua	NMPA approval	[55]
XOD Partial mechanism of action	Allopurinol	XOD	Inhibition of XOD reduced UA synthesis and reduced UA levels. Studies have shown that it may reduce the risk of AD through antioxidant and anti-inflammatory effects.	FDA, NMPA approval	[56,57]
	Febuxostat	XOD	Selectively inhibit XOD and reduce UA production. It was shown in AD animal models to alleviate neuroinflammation and OS, with neuroprotective effects.	FDA, NMPA approval	[57,58]
Other	Benzbromarone	URAT1	Inhibits URAT1 and promotes UA excretion. It rapidly reduces UA levels and has a strong anti-inflammatory effect.	NMPA approval	[59,60]

Table 2 Traditional Chinese Medicine for Alzheimer's Disease

Drug Category	Drug Name	Target Spot	Partial Mechanism of Action	Regulatory Status	Citation
Traditional Chinese medicine monomer	Flavonoids (apigenin, luteolin)	XOD, Aβ	In animal experiments, it can reduce neuroinflammation and Aβ deposition by inhibiting XOD, antioxidation, inhibiting the expression of TNF-α and IL-6, and regulating Aβ metabolism	Research progress	[61]
	Crocetin	Aβ, Tau	In animal experiments, the AMPK pathway mediated by stk11/lkb1 induces autophagy, promotes the clearance of Aβ, inhibits tau phosphorylation, resists oxidation, penetrates the BBB, and reduces neuroinflammation	Research progress	[62,63]
	Cistanche deserticola	PI3K-AkT, Tau	In the study of SAMP8 mouse AD model, Cistanche deserticola treatment group alleviated AD by increasing the expression of PI3K and Akt and decreasing the expression of p-tau/tau	Research progress	[64]

(*Continued*)

Table 2 (Continued).

Drug Category	Drug Name	Target Spot	Partial Mechanism of Action	Regulatory Status	Citation
Traditional Chinese medicine compound	Compound Cistanche Yizhi Capsules		A total of 120 patients with mild to moderate AD were treated for 6 months. Compared with the control group of donepezil hydrochloride tablets, the simple intelligence state scale and Barthel index rating scale scores of AD patients in the compound Congrong yizhi capsule treatment group were better, and AD symptoms were relieved	NMPA approval	[65]
	Huanglian Jiedu Decoction	Aβ1-42	In the clinical intervention study of 120 cases of AD patients, it was found that after treatment with Huanglian Jiedu Decoction, the patients' serum Aβ 1–42, TNF-α, etc. decreased, alleviated neuroinflammation, and slowed down the progression of AD	Research progress	[66]

Table 3 Drugs Commonly Used to Treat Alzheimer's Disease Nowadays

Drug Category	Drug Name	Target Spot	Partial Mechanism of Action	Regulatory Status	Citation
Cholinesterase inhibitors	Donepezil	Acetylcholinesterase(AChE)	Through reversible binding with ache, it can slow down the hydrolysis of acetylcholine, increase the concentration of synaptic ACh, and alleviate AD	FDA, NMPA approval	[67]
	Galantamine	AChE	Allosterically binds to the alpha subunit of nicotinic acetylcholine receptors and activates them, while competitively inhibiting ache and alleviating AD	FDA, NMPA approval	[67]
	Rivastigmine	AChE, Butyrylcholinesterase(BChE)	Non selective inhibitors of ache and BChE, combined at multiple sites, alleviate AD	FDA, NMPA approval	[68]
NMDA receptor antagonists	Memantine	NMDA receptor antagonists	Noncompetitive N-methyl-D-aspartate receptor (NMDAR) antagonists, alleviating AD	FDA, NMPA approval	[69]
	ZUNVEYL	AChE, NMDA	Inhibiting AChE activity to increase acetylcholine concentration while antagonizing NMDA receptor hyperactivation, improving cognitive function, and slowing down AD	FDA approval	[70]
Aβ monoclonal antibodies	Lecanemab	Aβ	In an 18 month, multicenter, double-blind Phase 3 trial of 1795 lecanemab subjects, it was found that lecanemab reduced Aβ markers in early AD patients and delayed AD	FDA, NMPA approval	[71]
	Donanemab	Aβ	Targeted binding of n3pg-Aβ oligomers activates antibody dependent cellular phagocytosis, reduces Aβ plaque burden, and slows AD	FDA, NMPA approval	[72]
Other	Tau immunotherapy	Tau	In the study of aged tau disease mouse model, intranasal administration induced trim21 mediated clearance of intracellular tau aggregates, reduced neurofibrillary tangles, improved cognitive function, and slowed down ad	Research progress	[73]

Discussion

The "bidirectionality" of UA in the development of AD constitutes the theoretical core contradiction, rooted in the "multifactorial nature" and "threshold ambiguity" of the UA curve. HUA has a bidirectional vicious cycle with chronic kidney disease, shares the core of insulin resistance with metabolic syndrome and promotes each other, and is also affected by gender-menopause. In existing experimental and clinical studies, it can only be concluded that UA has a bidirectional effect on the development of AD, without obtaining precise values and reference ranges. There are significant research differences in defining the protective UA concentration threshold, which, coupled with the interaction of individual genetic backgrounds and environmental factors, directly leads to inconsistent research results on the relationship between UA and AD.

Based on the above research, there are mainly the following reasons: Firstly, the limitations of animal models are significant. Typically, animal experiments exploring mechanisms often utilize experimental animals with targets similar to those in humans. The mechanisms and targets explored in long-term stable animal experiments are then applied to future clinical trials. Rodents contain UA-degrading enzymes, which have fundamentally different metabolic mechanisms from human UA. Furthermore, the human specificity of AD pathology (such as age-related heterogeneity) is difficult to simulate in animal models, making it impossible to directly extrapolate the conclusions of in vitro/animal experiments to humans. Secondly, clinical research designs are flawed. Most clinical studies rely on population samples of the disease, and to ensure accuracy, the data collected for comparison is as simple and easy to detect as possible. However, data collection for UA is often limited to short-term UA levels, which cannot reflect long-term dynamic changes. There are technical bottlenecks in 24-hour UA fluctuation monitoring, and large-sample cohort studies targeting AD are scarce. Without the support of a large number of UA and AD patients, it is difficult to obtain a reference range for "U-shaped" curve data. Insufficient control over confounding factors such as nutritional status and metabolic syndrome reduces the reliability of clinical evidence. Thirdly, UA has low solubility at physiological pH, limiting its direct clinical application. Although preclinical studies have shown that "supplementing precursors such as inosine to promote endogenous UA production" can enhance antioxidant effects, clinical verification is required.

Compared to existing AD treatment drugs, the positioning of UA-related interventions needs to be clear: the current mainstream anti-Aβ monoclonal antibodies (such as lenaclotide) are approved and can clear amyloid plaques and delay cognitive decline, but they have a high incidence of side effects (cerebral edema, microbleeds), require intravenous infusion, and are expensive; UA-related drugs are still in the early stages of clinical trials and have not been approved for AD treatment. Their advantage is that they exert their effects by antioxidizing, anti-inflammatory, and enhancing Aβ clearance. Moreover, existing urate-lowering drugs are safe, convenient to take orally, and low in cost, making them more suitable for AD prevention and early intervention. However, their shortcomings include the lack of large-scale Phase III clinical data, mild efficacy, and the difficulty in precise regulation of UA in the brain.

Conclusion

This study systematically elucidates the "U-shaped" association and bidirectional mechanism between UA levels and AD. The "U-shaped" curve is proposed in response to the heterogeneity of UA levels across populations. Both experimental and clinical studies have confirmed the bidirectional nature of UA: Physiological concentrations of UA exert neuroprotective effects through antioxidation, inhibition of neuroinflammation, regulation of autophagy, and protection of the BBB; abnormal concentrations of UA induce OS, activate inflammatory pathways, disrupt BBB integrity, and subsequently promote AD progression.

Existing AD drugs primarily target Aβ and tau proteins. UA as a monitorable endocrine indicator for AD patients, can complement the existing target gaps. If precise "U-shaped" curve ranges for UA are established for different age groups, genders, and AD stages in the future, UA may become a biomarker and a new treatment approach for AD prevention. However, current Chinese and Western medicine drugs that treat AD through the UA pathway (targeting UA metabolic enzymes and Aβ/tau proteins, respectively) have limitations.

To promote the application of UA in the prevention and treatment of AD, three major issues need to be addressed first: firstly, clarifying the concentration threshold and population heterogeneity at which UA exerts its effect; secondly,

maintaining benign UA levels through dietary intervention, lifestyle regulation, and medical intervention (such as precursor supplementation) to reduce AD risk; thirdly, strengthening large-sample clinical cohort studies to optimize the design of UA-related drug targets (such as metabolic enzymes, BBB transporters).

Future research and development can focus on three aspects: First, exogenous supplementation of UA to elevate its levels in the brain, breaking through the limitations of solubility and the BBB; second, exploring the "non-UA-lowering" neuroprotective effects of UA-lowering drugs such as allopurinol and febuxostat, expanding their indications; third, developing targeted approaches for BBB transporters such as GLUT9 and URAT1 to achieve precise regulation of UA in the brain. It should be noted that both anti-Aβ monoclonal antibodies and UA-related drugs face challenges such as difficulty penetrating the BBB, high heterogeneity in AD, and long clinical trial cycles. Therefore, a combined treatment approach that directly targets AD pathology (Aβ/tau) and utilizes UA for neuroprotection may be the optimal path to balance "potency" and "safety".

Acknowledgments

National Natural Science Foundation of China (No.: 81573135); Heilongjiang Natural Science Foundation Joint Guidance Project (No.: LH2023H056); Heilongjiang Postdoctoral Research Fund (No.: LBH-Q21042).

Disclosure

The authors report no conflicts of interest in this work, including disclosure of financial interests or other conflicts of interest.

References

1. Twarowski B, Herbet M. Inflammatory processes in Alzheimer's disease-pathomechanism, diagnosis and treatment: a review. *Int J Mol Sci*. 2023;24(7):6518. doi:10.3390/ijms24076518
2. Rostagno AA. Pathogenesis of Alzheimer's disease. *Int J Mol Sci*. 2022;24(1):107. doi:10.3390/ijms24010107
3. Husejko J, Kozakiewicz M, Gackowski M, et al. The influence of uric acid concentration on the daily functioning of patients at an advanced age, based on the results of selected point scales routinely used for the comprehensive geriatric assessment in Poland. *J Clin Med*. 2025;14(16):5793. doi:10.3390/jcm14165793
4. Husejko J, Kozakiewicz M, Gackowski M, et al. Higher uric acid associated with elevated IL-6 and IL-1β levels in older inpatients: a cross-sectional study. *Rheumatol Int*. 2025;45(8):177. doi:10.1007/s00296-025-05931-2
5. Socha E, Kośliński P, Koba M, et al. Amino acid levels as potential biomarker of elderly patients with dementia. *Brain Sciences*. 2020;10(12):914. doi:10.3390/brainsci10120914
6. Zhang Z, Bai J, Zhang S, et al. The relationship between Alzheimer's disease and pyroptosis and the intervention progress of traditional Chinese medicine. *Int J Gen Med*. 2024;17:4723–4732. doi:10.2147/IJGM.S478479
7. Furuhashi M. New insights into purine metabolism in metabolic diseases: role of xanthine oxidoreductase activity. *Am J Physiol Endocrinol Metab*. 2020;319(5):E827–E834. doi:10.1152/ajpendo.00378.2020
8. Wu D, Yang S, Yuan C, et al. Targeting purine metabolism-related enzymes for therapeutic intervention: a review from molecular mechanism to therapeutic breakthrough. *Int J Biol Macromol*. 2024;282(Pt 1):136828. doi:10.1016/j.ijbiomac.2024.136828
9. Xin D, Zhou J, Wu Z, et al. Research progress on uric acid excretion and related transporters in hyperuricemia. *Chin J General Pract*. 2023;1916–1922.
10. Adomako EA, Moe OW. Uric acid transport, transporters, and their pharmacological targeting. *Acta Physiologica*. 2023;238(2):e13980. doi:10.1111/apha.13980
11. Wang J, Chen Y, Zhong H, et al. The gut microbiota as a target to control hyperuricemia pathogenesis: potential mechanisms and therapeutic strategies. *Crit Rev Food Sci Nutr*. 2022;62(14):3979–3989. doi:10.1080/10408398.2021.1874287
12. Bao F, Yuan R, Shi Y, et al. Is it appropriate to adjust the uric acid reference interval? *Clin Lab*. 2024;70(4). doi:10.7754/Clin.Lab.2023.230914
13. Pascart T, A WK, Preda C, et al. The gout epidemic in French Polynesia: a modelling study of data from the Ma'i u'u epidemiological survey. *Lancet Glob Health*. 2024;12(4):e685–e696. doi:10.1016/S2214-109X(24)00012-3
14. Qiao M, Chen C, Liang Y, et al. The influence of serum uric acid level on Alzheimer's disease: a narrative review. *Biomed Res Int*. 2021;2021(1):5525710. doi:10.1155/2021/5525710
15. Wen S, Arakawa H, Tamai I. Uric acid in health and disease: from physiological functions to pathogenic mechanisms. *Pharmacol Ther*. 2024;256:108615. doi:10.1016/j.pharmthera.2024.108615
16. Kim JW, Byun MS, Yi D, et al. Serum uric acid, Alzheimer-related brain changes, and cognitive impairment. *Front Aging Neurosci*. 2020;12:160. doi:10.3389/fnagi.2020.00160
17. Scholefield M, Unwin RD, Cooper GJS. Shared perturbations in the metallome and metabolome of Alzheimer's, Parkinson's, huntington's, and dementia with Lewy bodies: a systematic review. *Ageing Res Rev*. 2020;63:101152. doi:10.1016/j.arr.2020.101152
18. Huang R, Tian S, Han J, et al. U-shaped association between serum uric acid levels and cognitive functions in patients with type 2 diabetes: a cross-sectional study. *J Alzheimers Dis*. 2019;69(1):135–144. doi:10.3233/JAD-181126
19. Bortolotti M, Polito L, G BM, et al. Xanthine oxidoreductase: a double-edged sword in neurological diseases. *Antioxidants*. 2025;14(4):483. doi:10.3390/antiox14040483

20. Liu L, Sun S. Correlation between serum bilirubin, blood uric acid and serum albumin and Alzheimer's disease. *J China Med Univ*. 2020;49(04):313–317.
21. Resende R, Fernandes T, C PA, et al. Endoplasmic reticulum-mitochondria contacts modulate reactive oxygen species-mediated signaling and oxidative stress in brain disorders: the key role of sigma-1 receptor. *Antioxid Redox Signal*. 2022;37(10–12):758–780. doi:10.1089/ars.2020.8231
22. Yang L-J, He J-B, Jiang Y, et al. Berberine hydrochloride inhibits migration ability via increasing inducible NO synthase and peroxynitrite in HTR-8/SVneo cells. *J. Ethnopharmacol*. 2023;305:116087. doi:10.1016/j.jep.2022.116087
23. Aerqin Q, Jia S-S, Shen X-N, et al. Serum uric acid levels in neurodegenerative disorders: a cross-sectional study. *J Alzheimers Dis*. 2022;90(2):761–773. doi:10.3233/JAD-220432
24. Pinz MP, Medeiros I, Carvalho LAC, et al. Is uric acid a true antioxidant? Identification of uric acid oxidation products and their biological effects. *Redox Rep*. 2025;30(1):2498105. doi:10.1080/13510002.2025.2498105
25. Boccardi V, Carino S, Marinelli E, et al. Uric acid and late-onset Alzheimer's disease: results from the ReGAl 2.0 project. *Aging Clin Exp Res*. 2021;33(2):361–366. doi:10.1007/s40520-020-01541-z
26. M TD, Niculescu A-G, I LI, et al. An overview of oxidative stress, neuroinflammation, and neurodegenerative diseases. *Int J Mol Sci*. 2022;23(11):5938. doi:10.3390/ijms23115938
27. Lowell CA. Hyperuricemia reduces neutrophil function. *Blood*. 2022;139(23):3354–3356. doi:10.1182/blood.2022016275
28. Ma Q, Honarpisheh M, Li C, et al. Soluble uric acid is an intrinsic negative regulator of monocyte activation in monosodium urate crystal-induced tissue inflammation. *J Immunol*. 2020;205(3):789–800. doi:10.4049/jimmunol.2000319
29. Wang Q, Zhao H, Gao Y, et al. Uric acid inhibits HMGB1-TLR4-NF-κB signaling to alleviate oxygen-glucose deprivation/reoxygenation injury of microglia. *Biochem Biophys Res Commun*. 2021;540:22–28. doi:10.1016/j.bbrc.2020.12.097
30. Gong Z, Huang J, Xu B, et al. Urolithin a attenuates memory impairment and neuroinflammation in APP/PS1 mice. *J Neuroinflammation*. 2019;16(1):62. doi:10.1186/s12974-019-1450-3
31. Li M, Sun T, Wu X, et al. Autophagy in the HTR-8/SVneo cell oxidative stress model is associated with the NLRP1 inflammasome. *Oxid Med Cell Longev*. 2021;2021(1):2353504. doi:10.1155/2021/2353504
32. Gu Z, Cao H, Zuo C, et al. TFEB in Alzheimer's disease: from molecular mechanisms to therapeutic implications. *Neurobiol Dis*. 2022;173:105855. doi:10.1016/j.nbd.2022.105855
33. Mijailovic NR, Vesic K, Borovcanin MM. The influence of serum uric acid on the brain and cognitive dysfunction. *Front Psychiatry*. 2022;13:828476. doi:10.3389/fpsyt.2022.828476
34. Xiao Q, Wang J, Tian Q, et al. Uric acid mitigates cognitive deficits via TFEB-mediated microglial autophagy in mice models of Alzheimer's disease. *Mol Neurobiol*. 2024;61(6):3678–3696. doi:10.1007/s12035-023-03818-6
35. Fang EF, Hou Y, Palikaras K, et al. Mitophagy inhibits amyloid-β and tau pathology and reverses cognitive deficits in models of Alzheimer's disease. *Nat Neurosci*. 2019;22(3):401–412. doi:10.1038/s41593-018-0332-9
36. Lamptey RNL, Chaulagain B, Trivedi R, et al. A review of the common neurodegenerative disorders: current therapeutic approaches and the potential role of nanotherapeutics. *Int J Mol Sci*. 2022;23(3):1851. doi:10.3390/ijms23031851
37. Aliena-Valero A, Baixauli-Martín J, Castelló-Ruiz M, et al. Effect of uric acid in animal models of ischemic stroke: a systematic review and meta-analysis. *J Cereb Blood Flow Metab*. 2021;41(4):707–722. doi:10.1177/0271678X20967459
38. Vila E, Solé M, Masip N, et al. Uric acid treatment after stroke modulates the krüppel-like factor 2-VEGF-a axis to protect brain endothelial cell functions: impact of hypertension. *Biochem Pharmacol*. 2019;164:115–128. doi:10.1016/j.bcp.2019.04.002
39. Guo H, Yang L, Song J, et al. Effects of MMP2/9 inhibitors on cognitive function and blood-brain barrier in mice with chronic cerebral ischemia. *Chin Soc Microcirc*. 2020;23–25.
40. Llull L, Amaro S, Á C. Administration of uric acid in the emergency treatment of acute ischemic stroke. *Curr Neurol Neurosci Rep*. 2016;16(1):4. doi:10.1007/s11910-015-0604-7
41. Cao B, Li Q, Xiong L, et al. Cerebrospinal fluid uric acid levels associated with disease severity in patients with anti-N-methyl-d-aspartate receptor encephalitis. *J Neuroimmunol*. 2023;384:578221. doi:10.1016/j.jneuroim.2023.578221
42. Heo SH, Lee S-H. High levels of serum uric acid are associated with silent brain infarction. *J Neurol Sci*. 2010;297(1–2):6–10. doi:10.1016/j.jns.2010.07.007
43. Al-Kuraishy HM, Jabir MS, Albuhadily AK, et al. The link between metabolic syndrome and Alzheimer disease: a mutual relationship and long rigorous investigation. *Ageing Res Rev*. 2023;91:102084. doi:10.1016/j.arr.2023.102084
44. Li D, Liu W, Zhou Z, et al. Effects of TLR4/NF-κB signaling pathway on renal function and urate crystallization in rats with uric acid nephropathy. *China J Trad Chin Med Inf*. 2021;28(09):56–61.
45. Tian T, Liu X, Li T, et al. Detrimental effects of long-term elevated serum uric acid on cognitive function in rats. *Sci Rep*. 2021;11(1):6732. doi:10.1038/s41598-021-86279-y
46. Xiao M. Serum uric acid and frailty. *Adv Clin Med*. 2024;14(05):2288–2293. doi:10.12677/acm.2024.1451684
47. Şanlı BA, Whittaker KJ, Motsi GK, et al. Unbiased metabolome screen links serum urate to risk of Alzheimer's disease. *Neurobiol Aging*. 2022;120:167–176. doi:10.1016/j.neurobiolaging.2022.09.004
48. Al-Kuraishy HM, Jabir MS, Al-Gareeb AI, et al. Evaluation and targeting of amyloid precursor protein (APP)/amyloid beta (aβ) axis in amyloidogenic and non-amyloidogenic pathways: a time outside the tunnel. *Ageing Res Rev*. 2023;92:102119. doi:10.1016/j.arr.2023.102119
49. Shao X, Lu W, Gao F, et al. Uric acid induces cognitive dysfunction through hippocampal inflammation in rodents and humans. *J Neurosci*. 2016;36(43):10990–11005. doi:10.1523/JNEUROSCI.1480-16.2016
50. Sefiani A, Geoffroy CG. The potential role of inflammation in modulating endogenous hippocampal neurogenesis after spinal cord injury. *Front Neurosci*. 2021;15:682259. doi:10.3389/fnins.2021.682259
51. Chen X, Mao Y, Guo Y, et al. LMP2 deficiency causes abnormal metabolism, oxidative stress, neuroinflammation, myelin loss and neurobehavioral dysfunctions. *J Transl Med*. 2023;21(1):226. doi:10.1186/s12967-023-04071-0
52. Cheng J, Zhang X, Xu Y, et al. Luteolin on gout and its mechanism. *Chin J Exp Pharm*. 2026;32(1):1–14. doi:10.13422/j.cnki.syfjx.20251705
53. Wu D, Niu J, Hu J, et al. Study on the anti hyperuricemia mechanism of total saponins from Plantago asiatica based on metabolomics and metagenomics. *Chin J Trad Chin Med*. In Press 2025. doi:10.19540/j.cnki.cjcmm.20250725.705

54. Wang Y, Liu H, Song Z, et al. Study on the effect of Wuling capsule in regulating intestinal flora against acute hyperuricemia. *Modern Chin Med*. In press 2025. doi:10.13313/j.issn.1673-4890.20250418004
55. Yuan Z, Zhang Z, Feng H, et al. Simiao Pill improved the intestinal barrier function of rats by regulating intestinal flora and up-regulated the expression of ABCG2 to promote ileal excretion of uric acid. *Chin J Exp Pharm*. 2026;32(1):101–112. doi:10.13422/j.cnki.syfjx.20251106
56. Fang N, Liwei L, Xiaoxi L, et al. Multidisciplinary expert consensus on the diagnosis and treatment of hyperuricemia-related diseases in China (2023 edition). *Chin J Pract Internal Med*. 2023;43(6):461–480.
57. Singh A, Singh K, Sharma A, et al. Past, present and future of xanthine oxidase inhibitors: design strategies, structural and pharmacological insights, patents and clinical trials. *RSC Med Chem*. 2023;14(11):2155–2191. doi:10.1039/D3MD00316G
58. Taha DE, Kabel AM, Yassin AI, et al. The potential mitigating effect of febuxostat alone or with donepezil on scopolamine-induced Alzheimer's disease in rats: the role of TXNIP/NLRP3 inflammasome signaling pathway. *Eur J Pharmacol*. 2025;1002:177875. doi:10.1016/j.ejphar.2025.177875
59. Wu F, Chen L, Du Y. Comparison of the efficacy and safety of benzbromarone and febuxostat in gout and hyperuricemia: a systematic review and meta-analysis. *Clin Rheumatol*. 2024;43(5):1745–1754. doi:10.1007/s10067-024-06933-4
60. Hou Z, Ma A, Mao J, et al. Overview of the pharmacokinetics and pharmacodynamics of URAT1 inhibitors for the treatment of hyperuricemia and gout. *Expert Opin Drug Metab Toxicol*. 2023;19(12):895–909. doi:10.1080/17425255.2023.2287477
61. Zhang Q, Yan Y. The role of natural flavonoids on neuroinflammation as a therapeutic target for Alzheimer's disease: a narrative review. *Neural Regen Res*. 2023;18(12):2582–2591. doi:10.4103/1673-5374.373680
62. Stefanoska K, Gajwani M, Tan ARP, et al. Alzheimer's disease: ablating single master site abolishes tau hyperphosphorylation. *Sci Adv*. 2022;8(27):eabl8809. doi:10.1126/sciadv.abl8809
63. Wani A, Al Rihani SB, Sharma A, et al. Crocetin promotes clearance of amyloid-β by inducing autophagy via the STK11/LKB1-mediated AMPK pathway. *Autophagy*. 2021;17(11):3813–3832. doi:10.1080/15548627.2021.1872187
64. Bu R, Zhang HL, Long S, et al. Exploring the mechanism of Cistanche in the treatment of Alzheimer's disease based on network pharmacology and experimental validation. *J Hainan Med Univ*. 2025;31(16):1229–1239+1253.
65. Hong L, Sun P, Yang Y, et al. The effect of compound Cistanche nourishing capsules in the treatment of mild to moderate Alzheimer's disease with liver and kidney deficiency and phlegm stasis obstruction. *China Medical Herald*. 2023;20(08):87–90.
66. He Y, Li S, Chang Y, et al. Effects of Coptis Jie Decoction on cognitive function and serum Aβ1-42 and BK expression in patients with Alzheimer's disease. *Chin J Trad Chin Med*. 2025;43(09):243–247.
67. Thawabteh AM, Ghanem AW, AbuMadi S, et al. Recent advances in therapeutics for the treatment of Alzheimer's disease. *Molecules*. 2024;29(21):5131. doi:10.3390/molecules29215131
68. Prešern U, Goličnik M, Bavec A. Genetic and functional dynamics of Butyrylcholinesterase in Alzheimer's disease: from mechanisms to clinical relevance. *Chem Biol Interact*. 2026;423:111809. doi:10.1016/j.cbi.2025.111809
69. Marotta G, Basagni F, Rosini M, et al. Memantine derivatives as multitarget agents in Alzheimer's disease. *Molecules*. 2020;25(17):4005. doi:10.3390/molecules25174005
70. Benzgalantamine (zunveyl) for Alzheimer's disease. *Med Lett Drugs Ther*. 2025;67(1726):59–60. doi:10.58347/tml.2025.1726b
71. Van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. *N Engl J Med*. 2023;388(1):9–21. doi:10.1056/NEJMoa2212948
72. Sims JR, Zimmer JA, Evans CD, et al. Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA*. 2023;330(6):512–527. doi:10.1001/jama.2023.13239
73. Gaikwad S, Puangmalai N, Sonawane M, et al. Nasal tau immunotherapy clears intracellular tau pathology and improves cognitive functions in aged tauopathy mice. *Sci Transl Med*. 2024;16(754):eadj5958. doi:10.1126/scitranslmed.adj5958