

Role of berberine in Alzheimer's disease

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Abstract: Berberine, an important protoberberine isoquinoline alkaloid, has several pharmacological activities, including antimicrobial, glucose- and cholesterol-lowering, antitumoral, and immunomodulatory properties. Substantial studies suggest that berberine may be beneficial to Alzheimer's disease (AD) by limiting the pathogenesis of extracellular amyloid plaques and intracellular neurofibrillary tangles. Increasing evidence has indicated that berberine exerts a protective role in atherosclerosis related to lipid- and glucose-lowering properties, implicating that berberine has the potential to inhibit these risk factors for AD. This review also attempts to discuss the pharmacological basis through which berberine may retard oxidative stress and neuroinflammation to exhibit its protective role in AD. Accordingly, berberine might be considered a potential therapeutic approach to prevent or delay the process of AD. However, more detailed investigations along with a safety assessment of berberine are warranted to clarify the role of berberine in limiting these risk factors and AD-related pathologies.

Keywords: berberine, amyloid, tau, oxidative stress, neuroinflammation, risk factors

Introduction

Alzheimer's disease (AD) is an irreversible devastating neurodegenerative disorder, which affects the growing aging population. It has been confirmed that AD is the most common cause of dementia among older adults who are slowly deprived of memory and thinking skills and eventually the ability to carry out the simplest tasks and thereby suffer from physical or mental dysfunction, cognitive impairment, and dementia. Since the first "Alzheimer's disease" patient, Auguste D, was reported in November 1906 in the 37th Meeting of South-West German Psychiatrists in Tübingen by the clinical psychiatrist and neuroanatomist Alois Alzheimer,¹⁻³ AD has had a research history of more than 100 years.^{3,4} Various pathogeneses of AD have been put forward. It is well known that extracellular amyloid plaques and intracellular neurofibrillary tangles (NFTs) are the two classic pathological features of AD.^{5,6} Other recognized pathological features include synaptic degeneration,⁷ hippocampal neuronal loss,⁸ neuroinflammation, and oxidative stress.⁹⁻¹¹

At present, several medications are used in research and clinical practice to intervene the progress of AD, such as donepezil, rivastigmine, and galantamine and memantine.¹²⁻¹⁴ They may be beneficial to maintain thinking in good run, slow memory loss, and improve communication skills and help with certain behavioral problems. However, it seems that all these drugs gave the same results, with limited effects, even no effects, and more side effects.¹⁵ Up to date, there are no medications that can prevent¹⁶ memory loss, cognitive impairment, and problems with learning, judgment, communication, and daily life. It is unlikely that none of the drugs can be successful for the cure of AD.¹⁴

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Berberine, an important protoberberine alkaloid, is widely used in traditional Chinese medicine for hundreds of years.¹⁷ Several therapeutic effects of berberine have been identified against cancer, obesity, congestive heart failure,¹⁸ inflammation, atherosclerosis, neurodegenerative diseases,¹⁹ rheumatoid arthritis, cardiovascular diseases,¹⁷ and metabolic disorders, such as dyslipidemia, impaired fasting glucose, metabolic syndrome, and diabetes.^{18,20–22} Neuroprotective effects of berberine on stroke models have been evidenced by in vitro and in vivo research data.^{23,24} Recent research found that berberine improved behavioral functional impairment via enhancing cortical neurogenesis after brain ischemia induced by permanent middle cerebral artery occlusion.²⁵ It has been found that berberine-mediated neuroprotection after ischemia is related to Akt/GSK3 β /ERK1/2 survival/apoptotic signaling pathway as well as JNK and Caspase-3 activity inhibition.^{26,27} Studies along the years have demonstrated its beneficial effect on stroke^{28–30} and various neurodegenerative and neuropsychiatric disorders.^{19,26,31–34} Furthermore, berberine was identified as a second-generation anti-AD drug acting as an inhibitor of human acetylcholinesterase according to computational screening of synthetic molecules and dietary phytochemicals, resulting in reduced level of acetylcholine neurotransmitters.³⁵ Hence, berberine will potentially be developed as a more effective therapeutic strategy for patients with AD.^{36,37}

This review focuses on the role of berberine in AD. An overview is provided for the proposed general pathogenic mechanism of berberine in AD via regulating amyloid and tau pathology. Emphasis is also laid on the observation that berberine is beneficial to AD undergoing the limitation of neuroinflammation and oxidative stress. This review also discusses that berberine may restrict the role of risk factors involved in the pathogenesis of AD. Finally, a perspective is made that berberine is possibly an effective potential drug for the prevention and treatment of AD.

Berberine

Berberine (molecular formula, C₂₀H₁₉NO₅ and molecular weight, 353.36 g/mol) is a bitter-tasting, yellow, plant alkaloid, with at least 3,000 years of medicinal use in Chinese and Ayurvedic medicine. Berberine has been identified in the roots, rhizomes, and stem bark of many plants, such as *Hydrastis canadensis* (goldenseal), *Coptis chinensis* (coptis or golden thread), *Berberis aquifolium* (Oregon grape), *Berberis vulgaris* (barberry), and *Berberis aristata* (tree turmeric). Historically, berberine has also been used as a yellow dye, due to its yellow color. In tradition, the main activity of berberine has been evidenced to possess antimicrobial properties against

various bacteria, fungi, protozoans, helminths, chlamydia, and viruses.^{38–41} In addition to this antimicrobial property, berberine has been found to have numerous pharmacological effects. Preliminary research suggests that berberine may improve the quality of life and decreased the mortality rates in patients with chronic congestive heart failure.^{42,43} Based on human and animal scientific research, berberine has been suggested to aid in glyce-mic regulation and in favor of the prevention and treatment of diabetes.^{44–46} Berberine has also been evaluated as a treatment for hypercholesterolemia, via reducing serum triglycerides, cholesterol, and low-density lipoprotein (LDL) cholesterol.^{47–49} Multiple studies have indicated that berberine has been found to be beneficial to cancer,⁵⁰ obesity, atherosclerosis,⁵¹ rheumatoid arthritis, cerebrovascular diseases, fever, headaches, high blood pressure, immune system, irritable bowel syndrome, leukemia, leukopenia, liver disease (alcoholic), osteoporosis, respiratory disorders, sedative, and so on.¹⁷ Berberine has been found to possess multiple neuroprotective effects and improve survival, development, and function of neurons, while protecting these electrically excitable brain cells.⁵² Furthermore, there has been strong evidence that berberine has a close relationship with neurodegenerative diseases,³⁴ including AD,³³ Parkinson's disease,⁵³ and Huntington's disease.³¹

Berberine and beta-amyloid pathology

One classic pathological hallmark of AD is the accumulation of beta-amyloid (A β) peptide derived from abnormal processing of amyloid precursor protein (APP). Various scientific research studies evidenced that the physiological generation of A β from sequential APP proteolysis is the most critical and intriguing process in the development of AD.^{54,55} APP is a transmembrane protein expressed at high levels in the brain and many tissues, concentrated in the synapses of neurons, and metabolized in a rapid and highly complex fashion by a series of sequential proteases, including α -secretase, β -secretase, and the intramembranous γ -secretase complex. Based on the physiological generation of A β from sequential APP proteolysis, the process of APP includes two pathways: the amyloidogenic pathway and the nonamyloidogenic pathway.^{56,57} In the amyloidogenic pathway, cleavage of APP by β -secretase generates soluble peptide APP β (sAPP β) and C-terminal fragment (C99). C99 can be cleaved by γ -secretase to yield the APP intracellular domain and A β . In the nonamyloidogenic pathway, α -secretase cleaves APP, generating a soluble fragment of APP (sAPP α) and C-terminal fragment, which is further cleaved by γ -secretase releasing the p3 peptide and APP intracellular domain.^{58–60}

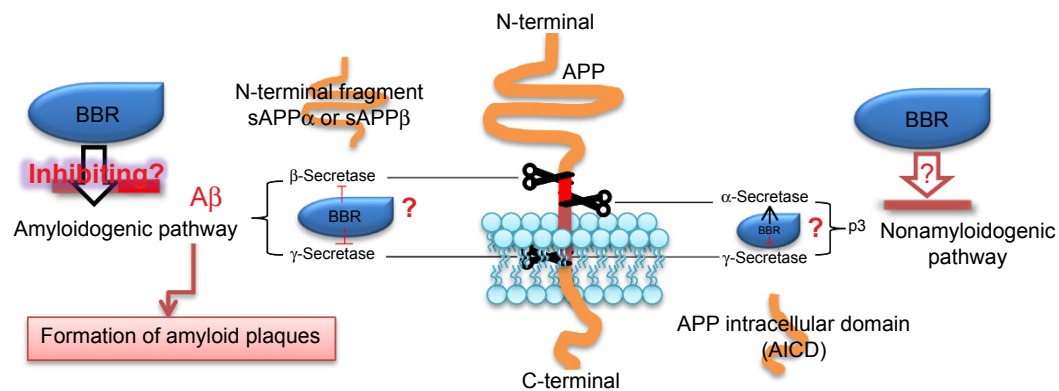


Figure 1 Possible mechanisms by which berberine modifies metabolism of APP.

Notes: In the amyloidogenic pathway, cleavage of APP by β-secretase generates soluble N-terminal fragment (sAPPβ) and C-terminal fragment (C99). C99 can be cleaved by γ-secretase to yield the APP intracellular domain (AICD) and Aβ. In the nonamyloidogenic pathway, α-secretase cleaves APP, generating a soluble fragment of APP (sAPPα) and C-terminal fragment (α-CTF), which is further cleaved by γ-secretase releasing the p3 peptide and AICD. BBR could decrease β-secretase and γ-secretase and inhibit the process of amyloidogenic pathway, lowering the Aβ release and the formation of amyloid plaques. The role of BBR in α-secretase remains unclear in the nonamyloidogenic pathway. ? Represent that the mechanism is unclear.

Abbreviations: BBR, berberine; Aβ, beta-amyloid; AICD, APP intracellular domain; APP, amyloid precursor protein; sAPP, soluble APP.

Recent studies suggested that the neurobiological effects of berberine may contribute to clinical benefits for AD by decreasing the generation of Aβ^{61,62} (Figure 1). An *in vitro* study demonstrated that berberine inhibited Aβ-stimulated production of interleukin-6 and monocyte chemoattractant protein-1 and downregulated the expression of cyclo-oxygenase-2 and induced nitric oxide synthase by blocking the phosphoinositide 3-kinase/protein kinase B and mitogen-activated protein kinase signaling pathways in primary microglial and BV2 cells.⁶³ Durairajan et al⁶⁴ demonstrated that berberine ameliorates Aβ pathology, gliosis, and cognitive impairment in an AD transgenic mouse model. In a rabbit model of AD, berberine treatment prevented the hippocampus from neurodegeneration, improved the behavior impairment, and lowered the activity of beta-site APP cleaving enzyme-1 (BACE-1).⁶⁵ Asai et al⁶⁶ found that berberine reduces Aβ levels by modulating APP processing in human neuroglioma H4 cells (stably expressing Swedish-type of APP) at the range of berberine concentration without cellular toxicity. It was reported that berberine decreased Aβ levels via inhibiting the activity of BACE-1,⁶⁷ which is a main β-secretase to determine the generation of Aβ. Zhu et al⁶⁸ reported that berberine decreases the production of Aβ_{40/42} by inhibiting the expression of BACE via activation of the ERK1/2 pathway in HEK293 cells. Although the previous studies have reported that berberine can decrease the production of Aβ, the mechanism remains unclear. Berberine can pass through the blood–brain barrier and has multiple pharmacological properties in the brain, including neuroprotective and neurotrophic effects.^{19,69,70} These data implicate that berberine would be a promising candidate for

modifying APP metabolism via regulating APP processing or Aβ clearance.

Berberine and tau pathology

It is well accepted that NFTs are a characteristic neuropathological lesion of AD. They are composed of a highly phosphorylated form of the microtubule-associated protein tau. Hyperphosphorylation of tau disrupts its normal function in regulating axonal transport and leads to the formation of NFTs and toxic species of soluble tau. It was reported that berberine attenuated tau hyperphosphorylation and cytotoxicity induced by Calyculin A, which impaired the axonal transport in neuroblastoma-2a cells.⁷¹ Furthermore, it was found that berberine performed a significant reduction of Calyculin A-induced tau hyperphosphorylation at Ser198/199/202, Ser396, Ser404, Thr205, and Thr231, and it also recovered the 2A activity of protein phosphatases and limited glycogen synthase kinase-3 beta (GSK-3β) activation, as determined by phosphatase activity assay and GSK-3β phosphorylation at Tyr216 and Ser9 of tau.⁷² The exact mechanism how berberine restrained the hyperphosphorylation of tau is still in exploration. In consideration that degradation of hyperphosphorylated tau by the proteasome is inhibited by the actions of Aβ, berberine may decrease the hyperphosphorylation of tau by limiting the actions of Aβ.

Berberine inhibits oxidative stress in AD

It is a general acceptance that oxidative stress plays an essential role in AD pathogenesis via the multifunctional pathway. Increasing persuasive research demonstrated that

berberine can limit the process of oxidative stress in the brain and central nervous system. Recent studies⁷³ have evidenced that berberine can treat senile dementia by regulating neurotransmitter, antioxidative stress, and neuroinflammation and affecting metabolism and other multitarget pathways. Hence, the hypothesis has been made that berberine may ameliorate oxidative stress in AD and play a neuroprotective role in AD pathogenesis and that it is a potential avenue for AD treatment.⁷³

Oxidative stress in AD

Oxidative stress has been proposed to be one of the most important factors in the pathogenesis of AD. Extensive oxidative research has been performed on the pathogenesis of AD over the past decade. A significant pathogenic feature is that oxidative stress may trigger an active, self-perpetuating cycle with chronic neuroinflammation while chronic neuroinflammation further promotes oxidative stress. Finally, this cycle may contribute to the occurrence of irreversible neuronal dysfunction and cell death in AD. Various studies have supported that oxidative stress is a culprit of cognitive impairment and dementia via destroying the connection of synapse in AD. There are abundant results indicating that the interaction between oxidative stress and neuroinflammation leads to A β generation and the formation of NFTs. A β production is a result of two sequential cleavages of the APP by two proteolytic enzymes, β -secretase and γ -secretase. Oxidative stress may upregulate β -secretase and γ -secretase and enhance A β production. Moreover, intracellular A β accumulation and the formation of NFTs contribute to a significant oxidative and inflammatory process that generates a vicious cycle between A β pathology and oxidation.

Berberine inhibits oxidative stress

A number of clinical and basic findings implicate that berberine is beneficial to a great variety of disorders via inhibiting the process of oxidative stress^{74–78} (Table 1). Berberine, the main active component of an ancient Chinese herb *Coptis chinensis Franch.*, has been used to treat diabetes for thousands of years.⁷⁹ Clinical and basic literature has implicated that berberine may serve as a new drug candidate in the treatment of diabetes on the basis of antioxidative stress by limiting the inflammatory parameters, antioxidative effect via down- and upregulation of GPx and CuZn-superoxide dismutase expression, strong potential to improve the oxidant–antioxidant balance, and inhibiting the activation of RhoA/ROCK signaling.^{80–88} Moreover, berberine has such an activity as a therapeutic agent for lipid lowering,

decreasing the level of serum cholesterol, triglycerides, and LDL cholesterol, which is associated with the inhibition of oxidation in mitochondria.^{79,89}

Berberine inhibits oxidative stress in AD

It has been evidenced the therapeutic potential of berberine in different neurodegenerative diseases such as AD, Parkinson's disease, and Huntington's disease.⁹⁰ Compelling research has demonstrated the beneficial role of berberine in neurodegenerative diseases, mainly due to its powerful antioxidant effect.³³ Several results indicate that berberine plays a neuroprotective role against AD via its antioxidative potential.^{73,91} The investigation conducted by Luo et al⁹¹ found the protective effects of berberine against A β -induced cell death in rat cortical neurons via decreasing the production of malondialdehyde and reactive oxygen species. Considering such an active, self-perpetuating cycle by which neuroinflammation interacts with oxidative stress, it is obvious that berberine may retard oxidative stress by limiting the neuroinflammation process in AD brain. In consideration that intracellular A β accumulation and the formation of NFTs contribute to a significant oxidative and inflammatory process that generates a vicious cycle, berberine may suppress the A β and tau pathologies to lower the progress of oxidative stress. However, the exact role of berberine in the oxidative stress in AD remains unclear. The mechanism of berberine in the pathogenesis of AD involved in oxidative damage is not well clarified. Therefore, it is essential to further clarify the mechanism of berberine in the pathogenesis of AD involved in oxidative damage.

Berberine retards neuroinflammation in AD?

Several research studies have implicated that inflammation is involved in the pathogenesis of AD, although it is still unclear exactly how inflammation plays a specific role in the course of the disease process.^{92,93} Since the late 1980s, the neuroinflammation hypothesis is supported by epidemiological retrospective observations and research from animal models, indicating that the chronic inflammation in AD enhances the disease process by various mechanisms.^{93,94} Numerous observations have shown the concept that berberine may be protective against the development of AD via inhibiting the vicious process of neuroinflammation.^{19,63,95}

Neuroinflammation in AD

A number of observations have evidenced the inflammatory processes in AD through multiple avenues. First,

Table 1 Berberine inhibits oxidative stress in diseases

Diseases	Possible antioxidative mechanism	References
Acute myocardial injury	Inhibiting the activity of LDH, CK, and MDA; declining the activity of SOD and CAT; reducing COX-2 and iNOS expression in I/R myocardium; and increasing HO-1 induction in human aortic endothelial cells	135
Aging	Reduction of ROS production and oxidative DNA damage; suppressing the level of constitutive mTOR- and DNA damage signaling; and reduction of the level of endogenous oxidants and constitutive DNA damage	136, 137
Alzheimer's disease	Reversing both the increase in malondialdehyde and the decrease in superoxide dismutase activity induced by Calyculin A	66, 72, 91
Atherosclerosis	Reducing oxidative stress and vascular inflammation and suppressing atherogenesis via a mechanism that includes stimulation of AMPK-dependent UCP2 expression	117
Cancer	Inhibiting reactive oxygen species generation and mitochondrial dysfunction	138–140
Cardiac failure	Downregulating phospholamban and exerting antioxidant activity	141
Cerebral ischemia diseases	Attenuating ROS production and increasing cell viability, antioxidant defense (GSH and SOD), and oxidant-sensitive proteins (HO-1 and Nrf2)	77, 125
Cognitive impairment	Mitigation of the oxidative stress burden	142, 109
Diabetes mellitus	The influence on oxidative stress markers (malondialdehyde, urinary 8-hydroxy-2'-deoxyguanosine, superoxide dismutase, aldose reductase, glutathione peroxidase, and total antioxidant capacity) and limiting the inflammatory parameters (vascular adhesion molecule-1, C-reactive protein and high-molecular-weight adiponectin); antioxidative effect via down- and upregulation of GPx and CuZn-SOD expression, respectively; strong potential to improve the oxidant–antioxidant balance; and inhibiting the activation of RhoA/ROCK signaling	80–88, 143–147
Hepatic fibrosis	Decreasing liver malondialdehyde concentration and increasing activities of liver superoxide dismutase, catalase, and glutathione peroxidase	148
Hepatic injury	Reducing apoptosis, which is possibly involved with the modulation of the PI3K/Akt/mTOR signaling pathway, and modulating antioxidant status and inflammatory cytokines	149–154
Hypertension	Limiting apoptosis and lowering expression of TLR4, Myd88, NF-κB, IL-6, and TNF-α; inhibiting endoplasmic reticulum stress; and subsequently scavenging ROS leading to COX-2 downregulation in carotid arteries	155, 156
Ischemic acute renal failure	Via intonation on apoptosis and mitochondrial-dependent pathway in renal ischemia reperfusion-induced mutilation	157
Kidney damage	The inhibition of oxidative/nitrosative stress, inflammation, autophagy, and apoptosis and the suppression of NF-κB signaling pathway	157–159
Liver disease	Inhibiting mitochondrial dysfunction, oxidative stress, and steatosis and activation of AMP-activated protein kinase	160–162
Metabolic syndrome	Inhibition of mitochondrial function, stimulation of glycolysis, activation of AMPK pathway, suppression of adipogenesis, and induction of LDL receptor expression	163
Parkinsonism	Neuroprotection in 6-OHDA-induced PD by protecting dopaminergic neurons and reducing the iron accumulation	164
Retinal degeneration	Diminishing oxidative stress in the retina	165

Abbreviations: AMPK, adenosine 5'-monophosphate-activated protein kinase; ATF, cAMP-dependent transcription factor; CAT, catalase; CK, creatine phosphokinase; HO-1, heme oxygenase-1; IL, interleukin; LDL, low-density lipoprotein; LDH, lactate dehydrogenase; MCP-1, monocyte chemotactic protein 1; MDA, malondialdehyde; MMP, matrix metalloproteinase; mTOR, mechanistic target of rapamycin; NF-κB, nuclear transcription factor kappa-light-chain-enhancer of activated B cells; Nrf2, nuclear factor erythroid 2 p45 related factor 2; ROS, reactive oxygen species; SOD, superoxide dismutase; TGF-β, transforming growth factor beta; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor-alpha; UCP2, uncoupling protein 2.

neuroinflammation contributes to Aβ pathology since it enhances Aβ generation and the failure of Aβ clearance.^{94,96} Second, the supportive evidence has suggested that inflammation in AD induces the formation of NFTs, resulting from increase in the excessive abnormal phosphorylation of tau.^{97,98} Third, clinical and basic data have demonstrated that cognitive decline and exaggerated behavior in AD may result in chronic neuroinflammation.^{99,100} Fourth, various studies have supported that a vicious cycle between neuroinflammation

and oxidative stress is a significant pathogenic feature in AD where the cycle may magnify the Aβ pathology and the abnormal phosphorylation of tau.^{101,102} Fifth, the low-level-lasting neuroinflammation in AD can be a marker of impaired adaptive immune responses leading to chronic inflammation, which induces the occurrence of AD-related following event, including the onset of cognitive impairment and dementia, the process of Aβ pathology, and the abnormal phosphorylation of tau.^{100,103}

Berberine retards inflammation

A growing body of evidence indicates that berberine retards inflammation, which is one of the pathological events in numerous disorders (Table 2). In addition to its own broad spectrum antimicrobial property, berberine has been reported to exert protective effects over various experimental models by inhibiting inflammation such as diabetes mellitus, obesity, heart diseases, cancers, cerebral ischemia, and hypertension (Table 2).

Berberine alleviates neuroinflammation in AD?

Extensive literature has pointed to the notion that berberine has the therapeutic potential in various neurodegenerative diseases by alleviating neuroinflammation.^{19,33,53,104} Convincing literature has demonstrated the beneficial role of berberine in

AD because of its anti-inflammatory properties.^{19,63} It has been believed that A β accumulation and tau hyperphosphorylation are the motivating factors of neuroinflammation in brain on the basis of numerous investigations.^{93,105,106} Therefore, it is inferred that berberine suspends the process of A β accumulation and tau hyperphosphorylation and then lowers the risk of neuroinflammation in AD brain. According to the vicious cycle that oxidative stress interacts with inflammation and each magnifies the pathological role in brain,^{98,99,107,108} it is believed that berberine suppresses the progression of oxidative stress and then achieves the effectiveness of bringing down neuroinflammation in AD. However, in the rat model of AD, which was established by injecting A β into the rat's hippocampuses bilaterally, berberine chloride (50 mg/kg) by intragastric administration can ameliorate the spatial memory impairment and increase the expression of IL-1 β

Table 2 Berberine retards inflammation in different disorders

Diseases	Possible anti-inflammation mechanism	References
Allergic rhinitis	Reducing allergic inflammation significantly	166
Alzheimer's disease	Reversing both the increase in MDA and the decrease in SOD activity induced by Calyculin A	66, 72, 91
Asthma	Inhibiting NF- κ B signaling pathway	167
Atherosclerosis	Reducing oxidative stress and vascular inflammation and suppressing atherogenesis via a mechanism that includes stimulation of AMPK-dependent UCP2 expression	117, 168
Cerebral ischemia diseases	Attenuating ROS production and increasing cell viability, antioxidant defense (GSH and SOD), and oxidant-sensitive proteins (HO-1 and Nrf2)	77, 125
Colon tumorigenesis	Through AMPK-dependent inhibition of mTOR activity and AMPK-independent inhibition of NF- κ B	169
Diabetes mellitus	Reducing oxidative stress	20, 87
Diabetic nephropathy	Inhibiting NF- κ B-driven renal inflammation and TGF- β /Smad3 signaling pathway	170, 171
Hepatic steatosis and nonalcoholic steatohepatitis	Suppressing endoplasmic reticulum stress	47, 172
Hypertension	Limiting expression of TLR4, Myd88, NF- κ B, IL-6, and TNF- α	155, 156
Irritable bowel syndrome	Reducing oxidative stress and inflammation response	173
Kidney injury	Suppressing NF- κ B signaling pathway	159
Metabolic syndrome	Inhibition of mitochondrial function, stimulation of glycolysis, activation of AMPK pathway, ATF-2 phosphorylation, and MMP-2 expression; suppression of adipogenesis and induction of LDL receptor expression	20, 163, 174
Mucus hypersecretion	Decreased the release of inflammatory cytokines TNF- α , IL-1 β , MCP-1, and inflammatory cells in bronchoalveolar lavage fluid	175
Myocardial ischemia/reperfusion injury	Reducing oxidative stress and inflammation response	176, 177
Obesity	Decreasing proinflammatory cytokines including TNF- α and IL-6	178
Osteoarthritis	Attenuating IL-1 β expression and inhibiting NF- κ B signaling pathway	179
Parkinson's disease	Reducing oxidative stress	19
Reflux esophagitis	Improving SOD and HO-1 levels	180
Retinal diseases	Decreasing oxidative stress and the activation of microglia/macrophages	165
Steatohepatitis	Against insulin resistance, inflammation, and lipid metabolism	181
Traumatic brain injury	Limiting the production of inflammatory mediators by glial cells	182
Ulcerative colitis	Inhibition of NF- κ Bp65 activation and increase in Nrf2 expression in colorectums	183

Abbreviations: AMPK, adenosine 5'-monophosphate-activated protein kinase; ATF, cAMP-dependent transcription factor; HO-1, heme oxygenase-1; IL, interleukin; LDL, low-density lipoprotein; LDH, lactate dehydrogenase; MCP-1, monocyte chemotactic protein 1; MDA, malondialdehyde; MMP, matrix metalloproteinase; mTOR, mechanistic target of rapamycin; NF- κ B, nuclear transcription factor kappa-light-chain-enhancer of activated B cells; Nrf2, nuclear factor erythroid 2 p45-related factor 2; ROS, reactive oxygen species; SOD, superoxide dismutase; TGF- β , transforming growth factor beta; TLR4, Toll-like receptor 4; TNF- α , tumor necrosis factor-alpha; UCP2, uncoupling protein 2.

and inducible nitric oxide synthase, and berberine might exaggerate the inflammation pathology.⁹⁵ Overall, the role of berberine in the neuroinflammation in AD is controversial. Hence, it is necessary to reveal the exact role of berberine in the neuroinflammation of AD in the near future.

Berberine decreases the role of risk factors in AD

Various research studies prove that a host of risk factors beyond genetics have a close relation with the pathogenesis of AD. Numerous results indicate the relationship between cognitive decline and vascular risk factors such as age, heart disease, stroke, hyperhomocysteinemia, hypertension, diabetes, and obesity. Thus, decreasing the role of these risk factors may reduce the risk of cognitive decline and AD.^{109,110}

It is well accepted that all these vascular risk factors contribute to the progress of atherosclerotic vascular diseases and the formation of atherosclerotic plaque, which is a common pathophysiology for cognitive decline, vascular dementia, and AD. Increasing literature demonstrated that berberine will prevent the progress of atherosclerosis development.^{111,112} The antiatherosclerosis mechanism of berberine may be associated with regulating lipids, anti-inflammation and oxidative stress, reducing blood sugar, and inhibiting vascular smooth muscle cell proliferation via regulating the intracellular Ca^{2+} handling of smooth muscle cells.^{113–116} The model of atherosclerotic vulnerable plaque was formed by placing a collar around the carotid artery in ApoE^{−/−} mice treated with homocysteine thiolactone. Berberine stabilizes atherosclerotic plaque in hyperhomocysteinemia ApoE^{−/−} mice by activating peroxisome proliferator-activated receptor gamma and inhibiting oxidative stress in endothelial cells.⁵¹ Recruitment of monocytes to endothelial cells plays a crucial role during early stages of atherosclerosis development. Berberine was found to markedly reduce oxidized LDL-induced monocyte adhesion to human umbilical vein endothelial cells through antioxidative activation of AMP-activated protein kinase and inhibition of RhoA/Rho kinase pathway.^{117,118} Berberine also decreased adhesion molecule expression, including VCAM1 and ICAM1. The previous results implicated that berberine plays a protective role in the early stages of atherosclerosis.¹¹⁹ Berberine inhibits serum-induced cholesterol accumulation and vascular smooth muscle cell proliferation and migration, improves neointima formation, and plays a novel potentially atheroprotective role in macrophages.^{120–122} Clinical data showed that combination therapy with berberine and atorvastatin was more effective in preventing atherosclerotic processes than atorvastatin

alone.¹²³ A new insight into berberine's molecular mechanism and its therapeutic potential in the treatment of atherosclerosis was confirmed by showing that berberine inhibits inflammation by promoting autophagy through activation of the AMPK/mTOR signaling pathway.¹²⁴

Basic research findings suggested that the combination of berberine with verapamil could enhance brain uptake of berberine and will provide a greater impact on neuroprotection in a rat model of transient global cerebral ischemia.¹²⁵ It was found that berberine dramatically lessened neurological deficits scores via increasing the activation of PI3K/Akt signaling and claudin-5 and decreasing NF- κ B expression in ischemic brain.^{126,127} It is found that berberine can decrease triglycerides, improve metabolic syndrome, have a better glycemic control in diabetes, and act directly on the vasculature to promote vascular health via its ability to activate adenosine monophosphate-activated kinase.¹²⁸ These compelling research data demonstrated that berberine may inhibit the pathogenesis of atherosclerosis and have the potential to reduce a host of risk factors for AD, helping people stay healthy as they age.

Conclusion and perspective

Various research studies have demonstrated that berberine, an isoquinoline alkaloid of the protoberberine type found in an array of plants, plays a neuroprotective role in the different neurological disorders including cerebral ischemic disorders,^{26,129–131} multiple sclerosis, and various neurodegenerative and neuropsychiatric disorders^{19,25,109,132} besides reducing risk for various cancers, osteoporosis, osteoarthritis, nonalcoholic fatty liver disease, and other disorders.^{78,128} Compelling evidence has indicated that berberine may be beneficial to AD by limiting the pathogenesis of extracellular amyloid plaques and intracellular NFTs. In addition that berberine may inhibit the pathogenesis of atherosclerosis and have the potential to reduce a host of risk factors for AD, berberine may also retard oxidative stress and neuroinflammation in the brain of AD. Accordingly, berberine may be a worthwhile drug to prevent or delay the process of AD.

There is substantial evidence from observational studies and clinical trials that conventional risk factors such as hypertension, diabetes, and dyslipidemia play a role in the development of AD. Targeting these risk factors will minimize the burden of AD in our aging population. Berberine can not only limit the role of these risk factors but also improve metabolic syndrome associated with AD as well. However, several studies have evaluated conflicting results

that berberine enhances the development of atherosclerosis and foam cell formation by inducing scavenger receptor-A expression in macrophage¹³³ and berberine-reduced apoptosis, HIF-1 α , and p53 in cerebral tissue of middle cerebral artery occlusion rats.¹³⁴ Therefore, the exact neuroprotective role of berberine remains indistinct. Despite that berberine may be a promising target to prevent and treat AD in the future on the basis of basic molecular biology research and clinical trials, further research is needed to clarify the role of berberine in limiting these risk factors and AD-related pathologies.

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Disclosure

The authors report no conflicts of interest in this work.

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