

# Potential Applications of Natural Components of Traditional Chinese Medicine Delivery via Nanoparticle Drug Delivery Systems in the Treatment of Alzheimer's Disease

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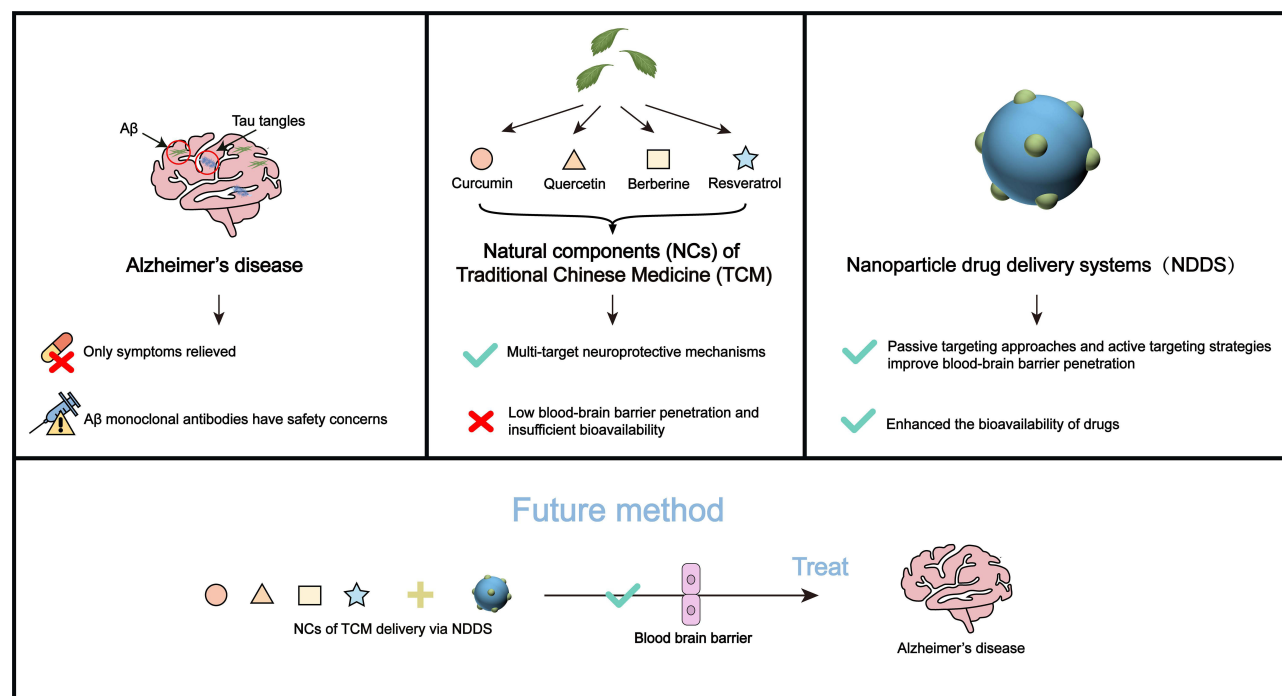
**Abstract:** Alzheimer's disease (AD), a primary neurodegenerative disorder, is characterized by amyloid- $\beta$  plaques and tau hyperphosphorylation-induced neurofibrillary tangles. Current treatments only alleviate symptoms, and A $\beta$  monoclonal antibodies raise safety concerns in clinical use. Natural components (NCs) of Traditional Chinese Medicine (TCM) (eg, curcumin, quercetin, berberine, resveratrol) exhibit multi-target neuroprotective effects in AD, but poor blood-brain barrier (BBB) penetration and low bioavailability limit clinical use. Recent strategies to enhance TCM delivery include NP-based nanoparticle (NP) drug delivery systems (NDDS), structural modifications, and combination therapies. NDDS demonstrate superior performance in enabling brain-targeting delivery via passive (paracellular/transcellular) and active (adsorption-/receptor-/carrier-mediated transcytosis) approaches, improving NCs' stability, controlled release, and bioavailability. With NCs of TCM delivery via NDDS, it is possible to develop intelligent therapeutic systems that combine multi-target regulation with precise drug delivery. This review summarizes the diverse neuroprotective effects of NCs of TCM in AD treatment and discusses the commonly used types of NPs for AD therapy. It particularly focuses on these NCs of TCM delivery via NDDS, covering aspects such as NPs types, fabrication techniques, characteristics, administration routes, and advantages. Finally, the challenges and potential solutions for NCs of TCM were examined, along with comparative advantages and limitations among different NPs and future research directions. Collectively, NCs of TCM delivery via NDDS demonstrate promising therapeutic potential for AD treatment.

**Keywords:** Alzheimer's disease, Traditional Chinese Medicine, natural components, nanoparticle drug delivery systems

## Introduction

Alzheimer's disease (AD), the primary cause of dementia, accounts for 60–80% of global dementia cases, affecting nearly 50 million people.<sup>1</sup> This number is expected to nearly double to 115 million by 2050, primarily due to aging populations, particularly in low- and middle-income countries.<sup>2,3</sup> AD is characterized by progressive cognitive decline, memory loss, and, in advanced stages, personality changes and language impairments.<sup>4</sup> While the precise mechanisms remain elusive, key pathological features include the accumulation of  $\beta$ -amyloid (A $\beta$ ) plaques, hyperphosphorylation of tau proteins leading to neurofibrillary tangles, and substantial neuronal and synaptic loss.<sup>2</sup> Current treatments, such as cholinesterase inhibitors (eg, donepezil), N-Methyl-D-Aspartate receptor antagonists (eg, memantine), and medications targeting neuropsychiatric symptoms, provide only limited relief and often present significant side effects. Though newer drugs, including aducanumab and lecanemab, have been approved, their high costs and safety concerns restrict their

## Graphical Abstract



accessibility.<sup>5,6</sup> Therefore, the development of safe, affordable, and effective therapies remains crucial for improving the outcomes of patients with AD.

Traditional Chinese medicine (TCM) has been employed in the treatment of central nervous system (CNS) disorders for over two millennia.<sup>7</sup> In AD, various natural components (NCs) of TCM, such as curcumin (Cur), quercetin (QT), berberine (BBR), and resveratrol (RES), have demonstrated considerable neuroprotective effects. Their mechanisms primarily involve inhibiting  $A\beta$  production and aggregation, modulating tau protein hyperphosphorylation, suppressing acetylcholinesterase (AChE) activity, and exerting antioxidant and anti-inflammatory actions. However, the clinical applicability of these NCs is hindered by their poor oral bioavailability and the restrictive nature of the blood-brain barrier (BBB), which prevents sufficient CNS concentrations and limits their therapeutic effectiveness. Consequently, enhancing the bioavailability and brain delivery efficiency of TCM has become a pivotal research focus.

Recent studies have explored various strategies to address these challenges, including nanoparticle (NP) drug delivery systems (NDDS), structural modifications of NCs, and combination therapies. Among these, NP-based NDDS have gained widespread use in disease treatment, offering innovative solutions to overcome the limitations of conventional drugs.<sup>8–10</sup> NPs, as drug carriers, offer numerous advantages, including improved bioavailability, targeted delivery, enhanced drug concentration at the site of action, and reduced side effects.<sup>11–13</sup> Additionally, NPs can traverse the BBB via active or passive targeting mechanisms, facilitating efficient CNS delivery.<sup>14–16</sup> The feasibility of NDDS in AD treatment has been validated in numerous studies.<sup>16–18</sup> Thus, employing NPs to deliver NCs of TCM not only enhances the multi-target therapeutic potential of these compounds but also significantly improves their efficacy, making this approach a highly promising strategy.

This review examined the neuroprotective effects of TCM in AD, focusing on the inhibition of  $A\beta$  generation and deposition, alleviation of tau protein hyperphosphorylation, suppression of AChE activity, and reduction of oxidative stress and neuroinflammation. The review further explored the types of NPs commonly used in AD treatment and highlights advancements in the delivery of TCM-derived NCs through NDDS. Key topics include the types of nanomedicines, fabrication processes, properties, routes of administration, and their respective advantages. Finally, the

challenges and potential solutions for improving the delivery of NCs of TCM were discussed, alongside a comparison of the advantages and limitations of different NP types and future research directions.

## The Neuroprotective Effect of Natural Components of Traditional Chinese Medicine on Alzheimer's Disease

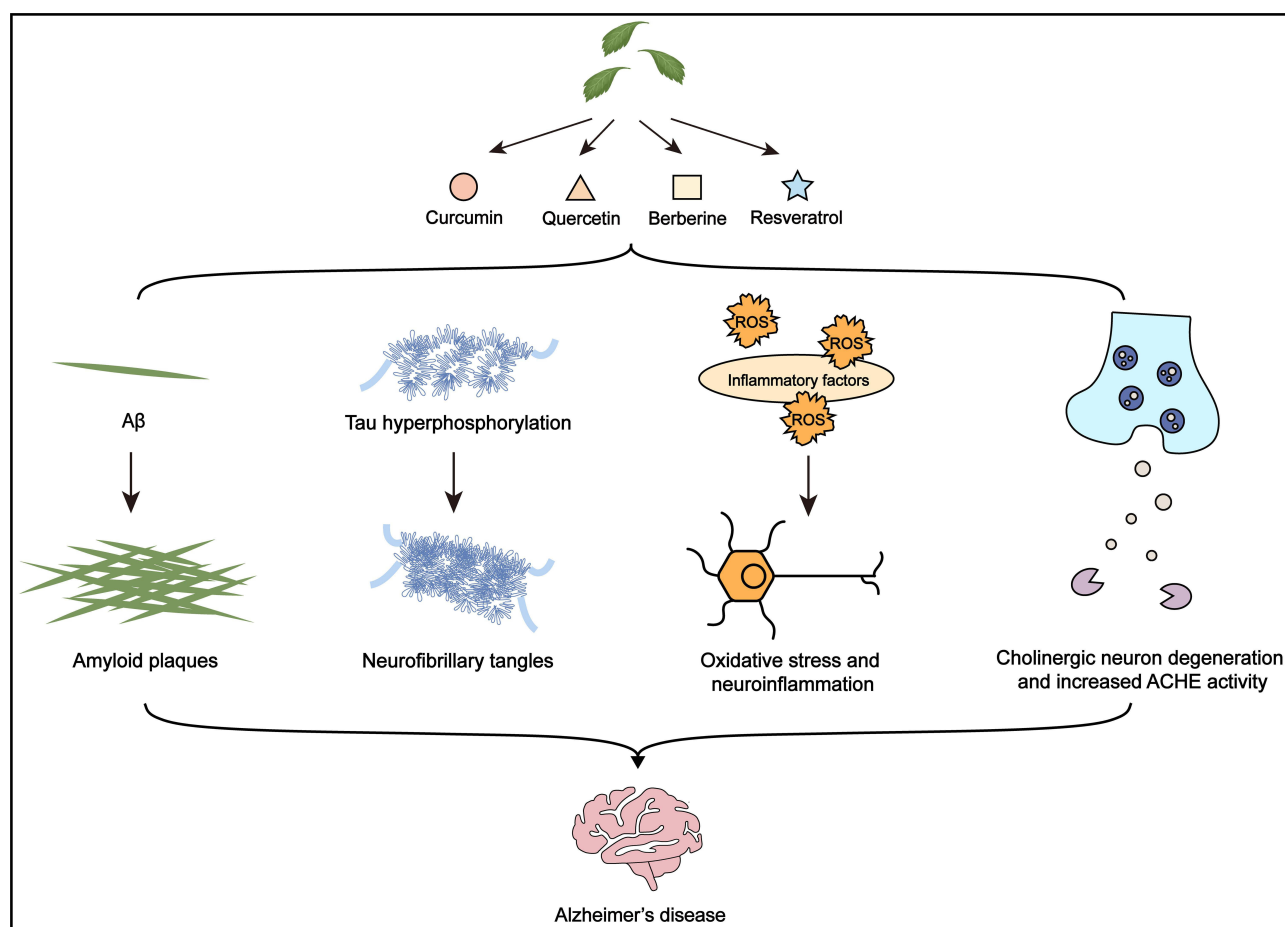
AD is a neurodegenerative disorder driven by multiple pathological mechanisms,<sup>19</sup> including: 1) A $\beta$  accumulation and deposition: Under normal physiological conditions, amyloid precursor protein (APP) is cleaved via the  $\alpha$ -secretase/ $\gamma$ -secretase pathway. However, aberrant cleavage through the  $\beta$ -secretase (BACE1)/ $\gamma$ -secretase pathway results in the production of A $\beta$ , which is secreted from cells and eventually aggregates into amyloid plaques.<sup>20</sup> 2) Tau hyperphosphorylation: In pathological conditions, excessive or abnormal phosphorylation of tau protein impedes its ability to assemble into microtubules, destabilizing the microtubule network, leading to depolymerization and axonal dysfunction, which in turn causes neuronal degeneration.<sup>21</sup> 3) Oxidative stress: This arises from an imbalance between pro-oxidants and antioxidants in the body. The brain, with its high oxygen consumption and relatively low antioxidant defense, is particularly vulnerable to oxidative damage. Persistent redox imbalance accelerates disease progression, contributing to the core neuropathological features of AD, such as neuronal degeneration, protein aggregates (including A $\beta$  plaques and tau tangles), and neuroinflammation.<sup>22</sup> Inflammation exacerbates neuronal damage, leading to cellular dysfunction and eventual neuronal death.<sup>23</sup> 4) Cholinergic neuronal degeneration: Cholinergic neurons, which secrete acetylcholine (ACh) vital for learning and memory, undergo degeneration in AD, reducing ACh levels.<sup>24</sup> Additionally, elevated AChE activity further shortens ACh's half-life.<sup>25,26</sup>

Emerging research indicates that these pathological mechanisms are interrelated. For instance, A $\beta$  can trigger tauopathy, oxidative stress, and inflammation,<sup>27,28</sup> while oxidative stress and inflammation exacerbate the production and aggregation of A $\beta$  and tau.<sup>29</sup> Consequently, therapeutic approaches should adopt a multi-target strategy rather than focusing on a single mechanism. Nanocarriers (NCs) derived from TCM, such as Cur, QT, BBR, and RES, exhibit various neuroprotective effects, including reducing A $\beta$  accumulation, mitigating tau hyperphosphorylation, inhibiting AChE activity, and alleviating oxidative stress and neuroinflammation (Figure 1).<sup>26,30–33</sup> However, the exact mechanisms underlying these neuroprotective effects remain unclear, necessitating further investigation into the pharmacological potential of TCM-based NCs. This section explores several TCM-derived NCs and their neuroprotective effects in AD (Table 1).

## The Neuroprotective Effect of Curcumin on Alzheimer's Disease

Numerous studies suggest that Cur offers neuroprotective benefits by reducing the formation and aggregation of A $\beta$ . Zhang et al examined the effects of Cur on A $\beta$  levels and APP processing in primary cortical neurons from mice and various cell lines.<sup>34</sup> Their findings demonstrated that Cur effectively lowered A $\beta$  levels by impairing APP maturation in the secretory pathway. Increasing evidence highlights the potential of activating the Wnt/ $\beta$ -catenin signaling pathway for neuroprotection in AD.<sup>80</sup> Moreover, A $\beta$  induces the downregulation of this pathway, contributing to disease progression. Cur has been shown to reduce A $\beta$  generation and accumulation in a concentration- and time-dependent manner by activating the Wnt/ $\beta$ -catenin pathway, with this activation occurring via inhibition of glycogen synthase kinase-3 beta (GSK-3 $\beta$ ) activity.<sup>35</sup> Notably, presenilin 1 (PS1), a substrate of GSK-3 $\beta$  and an essential component of  $\gamma$ -secretase, is involved in this process, ultimately reducing A $\beta$  production. In AD, impaired autophagy hampers A $\beta$  clearance, exacerbating disease progression. Enhancing autophagy to promote A $\beta$  clearance is a promising therapeutic strategy. Furthermore, the inhibition of mammalian target of rapamycin (mTOR) has been shown to positively regulate autophagy, with mTOR being primarily controlled by the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/mTOR signaling pathway.<sup>81</sup> While Cur's anti-cancer effects, achieved through inhibition of the PI3K/Akt/mTOR pathway, are well-documented, its potential for treating AD via this mechanism remains unclear. Wang et al investigated Cur's effects on autophagy in APP/PS1 double transgenic mice, finding that Cur downregulated the PI3K/Akt/mTOR signaling pathway, thereby enhancing autophagy and facilitating A $\beta$  clearance.<sup>36</sup>

Further studies suggest that Akt activation can inhibit GSK-3 $\beta$  activity, thereby reducing tau hyperphosphorylation. SoukhakLari et al observed that Cur, particularly at doses of 50 and 100 mg/kg, prevented scopolamine-induced memory



**Figure 1** Neuroprotective effect of Traditional Chinese Medicine on Alzheimer's disease.

impairment in mice.<sup>37</sup> This protective effect was attributed to Akt activation and GSK-3 $\beta$  inactivation. These findings were corroborated by Wang et al, who demonstrated that combining Cur with exosomes enhances its bioavailability and improves cognitive deficits in mice induced by OA.<sup>38</sup> Additionally, Caveolin-1 has been implicated in GSK-3 $\beta$ -related signaling. Sun et al investigated the expression levels of Caveolin-1, GSK-3 $\beta$ , and tau following Cur treatment to explore potential mechanisms.<sup>39</sup> The results suggest that Cur may reduce tau hyperphosphorylation in the brains of AD mice by inhibiting the Caveolin-1/GSK-3 $\beta$  pathway.

The effects of Cur on oxidative stress and inflammation have been extensively investigated. Over 20 years ago, Lim et al explored the neuroprotective effects of two different Cur doses (160 ppm and 5000 ppm) in mice with AD.<sup>40</sup> Their findings indicated that both doses reduced oxidative damage and inhibited the inflammatory cytokine interleukin-1 (IL-1) without significant side effects. Notably, the lower dose of Cur further decreased A $\beta$  levels by approximately 43–50%. A $\beta$  is known to activate microglia, leading to the production of inflammatory cytokines. While Cur has been shown to inhibit lipopolysaccharide (LPS)-induced microglial activation, its effects on A $\beta$ -induced microglial activation remain unclear. To address this, Shi et al examined the impact of Cur on A $\beta$ -induced microglial activation.<sup>41</sup> Their results demonstrated that Cur inhibited microglial activation and downregulated IL-1, interleukin-6 (IL-6), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) levels, with this effect being positively correlated with Cur dose. Further studies suggested that this inhibition might be mediated through the phosphorylation of ERK1/2 and P38. Cur also activates peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ), which has been shown to suppress neuroinflammation induced by cerebral ischemia. However, its role in AD remains less understood. Liu et al demonstrated that Cur enhances PPAR $\gamma$  activity, inhibits the nuclear factor kappa-B (NF- $\kappa$ B) pathway, and alleviates neuroinflammatory responses.<sup>42</sup> Additionally, Cur activates the adenosine 5'-monophosphate-activated protein kinase (AMPK) pathway, thereby inhibiting inflammation and oxidative stress. Specifically, Cur promotes the phosphorylation of AMPK in the brains of

**Table 1** The Neuroprotective Effects of Different Traditional Chinese Medicines

Traditional Chinese Medicines	Experimental Models (in vitro / in vivo)	Route of Administration	Dose	Key Findings	References
Curcumin	In vitro: H4-APP751, B104-APP751, CHO-APP751, E18,	Cell culture	1–20 $\mu$ M	Curcumin effectively lowered A $\beta$ levels by impairing the maturation of APP in the secretory pathway	[34]
	In vitro: Plasmid APPswe and BACE1-myhis were transiently co-transfected into SH-SY5Y cells	Cell culture	1–20 $\mu$ M	Curcumin reduces A $\beta$ generation and accumulation in a concentration- and time-dependent manner by activating the Wnt/ $\beta$ -catenin signaling pathway	[35]
	In vivo: APP/PS1 double transgenic AD mice	Oral	160 ppm	Curcumin induces downregulation of the PI3K/Akt/mTOR signaling pathway, enhancing autophagy and A $\beta$ clearance	[36]
	In vivo: Scopolamine-induced in male NMRI mice; In vivo: OA-induced in C57BL/6 mice	Oral; Intraperitoneal	50 and 100 mg/kg; 0.1 mg/mL	Curcumin can prevent scopolamine or OA-induced memory impairment in mice via Akt/GSK-3 $\beta$ signaling pathway	[37, 38]
	In vivo: APP/PS1 double transgenic AD mice	Oral	0.16 g/kg and 1.0 g/kg	Curcumin may reduce tau hyperphosphorylation in the brains of AD mice by inhibiting the Caveolin-1/GSK-3 $\beta$ pathway	[39]
	In vivo: Alzheimer transgenic APPSw micel (Tg2576)	Oral	160 ppm and 5000 ppm	1. Curcumin reduced oxidative damage and inhibited the inflammatory cytokine IL-1 without causing significant side effects; 2. The lower dose of curcumin further decreased A $\beta$ levels by approximately 43–50%	[40]
	In vitro: Primary mouse microglia	Cell culture	10 $\mu$ M	1. Curcumin inhibited microglial activation and downregulated the levels of IL-1, IL-6, and TNF- $\alpha$ ; 2. This effect was positively correlated with the dose of curcumin; 3. This inhibition may occur through the involvement of ERK1/2 and P38 phosphorylation	[41]
	In vitro: Primary hippocampus neuronal; In vivo: APP/PS1 transgenic mice	In vitro: Cell culture; In vivo: Intraperitoneal	In vitro: 10 $\mu$ M; In vivo: 150 mg/kg	Curcumin enhances PPAR $\gamma$ activity, suppresses the NF- $\kappa$ B pathway, and alleviates neuroinflammatory responses	[42]
	In vivo: A $\beta$ (1–42)-induced in C57BL/6 mice	Oral	150 mg/kg	Curcumin promotes the phosphorylation of AMPK in the brains of AD mice, leading to a reduction in inflammatory factors (TNF- $\alpha$ , IL-6, IL-1 $\beta$ ) and an increase in SOD levels	[43]
	In vivo: Scopolamine-induced in male Sprague–Dawley rats	Oral	3–10 mg/kg	The inhibition of AChE increased with higher doses cur ranging from 3 to 10 mg/kg	[44]
	In vivo: Cadmium-induced in male albino rats	Intraperitoneal	12.5 and 25 mg/kg; 25 and 50 mg/kg	1. The inhibition of AChE increased with higher doses cur ranging from 12.5 and 25 mg/kg; 2. No significant difference in AChE inhibition with Cur doses between 25 and 50 mg/kg	[45, 46]

(Continued)

Table I (Continued).

Traditional Chinese Medicines	Experimental Models (in vitro / in vivo)	Route of Administration	Dose	Key Findings	References
Quercetin	In vivo: 3xTg (PS1M146V knock-in, APPswe, taup301L)-AD mice	Intraperitoneal; Oral	25 mg/kg; 100 mg/kg	Quercetin reduced levels of A $\beta$	[47, 48]
	In vivo: Aluminum chloride-induced in male Wistar rats	Oral	25 and 50 mg/kg	Quercetin might reduce A $\beta$ aggregation in aluminum chloride-induced AD rats by upregulating the expression of the ADAM10 and ADAM17 genes	[49]
	In vitro: OA-induced in HT22 cells	Cell culture	5 and 10 $\mu$ M	Quercetin reduced OA-induced hyperphosphorylation of tau protein through the PI3K/Akt/GSK3 $\beta$ signaling pathway	[50]
	In vitro: A $\beta$ (1-42)-induced in primary rat neuronal cells	Cell culture	5–40 $\mu$ M	1. At higher concentrations (20 and 40 $\mu$ M), Quercetin indicated antioxidant activity and not observed at lower concentrations (5 and 10 $\mu$ M); 2. Quercetin reduced A $\beta$ neurotoxicity at both lower (5 and 10 $\mu$ M) and higher (20 and 40 $\mu$ M) concentrations, no significant difference was observed between the concentration groups	[51]
	In vivo: APP/PS1 double transgenic AD mice	Intragastric	100mg/kg	1. Quercetin may enhance cognitive abilities in AD mice by increasing levels of GSH, MDA, and SOD while reducing ROS levels; 2. Quercetin activated the Keap1/Nrf2/HO-1 pathway to play an antioxidant role	[52]
	In vivo: A $\beta$ (1-42)-induced in male BALB/c mice	Intranasal	30 and 100 mg/kg	Treatment with Quercetin significantly reduced both GFAP and pro-inflammatory cytokine levels in a dose-dependent manner within the 30–100 mg/kg range	[33]
	In vivo: Cadmium-induced in male Wistar rats	Oral	5, 25, and 50 mg/kg	QT (at doses of 5, 25, and 50 mg/kg) reduced AChE activity by 23%, 49%, and 54%, respectively	[53]
	In vivo: Streptozotocin-induced in male Wistar rats	Intraperitoneal	5, 25, and 50 mg/kg	A dose of 50mg/kg of QT prevents diabetes-induced increases in cortical and hippocampal AChE activity	[54]

Berberine	In vivo: APP/PS1 transgenic mice	Oral	260mg/kg	Berberine reduced the production and accumulation of A $\beta$ by inhibiting the activity of BACE1	[55]
	In vivo: APP/PS1 transgenic mice	Intragastric	50 and 100 mg/kg	Berberine enhanced $\alpha$ -secretase activity, reducing A $\beta$ levels in the hippocampus of AD mice	[56]
	In vivo: 3xTg (PS1M146V knock-in, APPswe, tauP301L)-AD mice	Oral	50 and 100 mg/kg	Berberine activated autophagy through the class III PI3K/Beclin1 signaling pathways to enhance A $\beta$ clearance	[57]
	In vivo: APP/PS1 transgenic mice	Intragastric	50 and 100 mg/kg	Berberine activated autophagy through the AMPK/mTOR signaling pathways to enhance A $\beta$ clearance	[58]
	In vivo: 3xTg (PS1M146V knock-in, APPswe, tauP301L)-AD mice	Oral	100 mg/kg	1. Berberine reduces tau hyperphosphorylation by regulating the activity of AKT/GSK-3 $\beta$ ; 2. Berberine enhanced autophagy activity via the class III PI3K/Beclin1 pathway and promoted tau clearance	[59]
	In vitro: Calyculin-induced in AHEK293 cells; In vitro: Calyculin-induced in N2a cells	Cell culture	20 $\mu$ g/mL; 5–100 $\mu$ g/mL	Berberine reduced tau hyperphosphorylation by enhancing PP2A activity and decreasing GSK-3 activity	[60, 61]
	In vitro: H <sub>2</sub> O <sub>2</sub> -induced in NSC34 cells; In vivo: 3xTg (PS1M146V knock-in, APPswe, tauP301L)-AD mice; In vivo: Establishment of stroke mouse model by MCAO surgery	In vitro: Cell culture; In vivo: Oral; In vivo: Intragastric	In vitro: 0.1–10 nM; In vivo: 50 mg/kg; In vivo: 10, 20 and 50 mg/kg	Berberine might exert antioxidant effects by activating Nrf2 to regulate GSH, GPX4, HO-1	[62–64]
	In vivo: Lipopolysaccharide-induced in male albino Wistar rats	Oral	10 and 50 mg/kg	Berberine inhibited the NF- $\kappa$ B signaling pathway and reduced inflammatory cytokines in AD mice	[65]
	In vitro: Lipopolysaccharide-induced in BV-2 cells	Cell culture	1–10 mM	Berberine could inhibit the neuroinflammatory response of microglia by targeting the AMPK pathway	[66]
	In vitro: SH-SY5Y cells; In vivo: Streptozotocin-induced in male Wistar rats; In vivo: Scopolamine-induced in male Sprague-Dawley rats	In vitro: Cell culture; In vivo: Oral; In vivo: Intraperitoneal	In vitro: 0.1–1000 $\mu$ M; In vivo: 50 and 100 mg/kg; In vivo: 20 mg/kg	Berberine could inhibit AChE activity	[67–69]

(Continued)

Table I (Continued).

Traditional Chinese Medicines	Experimental Models (in vitro / in vivo)	Route of Administration	Dose	Key Findings	References
Resveratrol	In vitro: APP695-transfected HEK293 cells, APP695-transfected N2a cells	Oral	40 $\mu$ M	Resveratrol inhibited A $\beta$ generation through proteasome-mediated mechanisms	[70]
	In vitro: Baculovirus-expressed BACE1	Virus culture	0.34–19.8 $\mu$ M	Resveratrol reduced A $\beta$ production by inhibiting BACE1	[71]
	In vitro: HEK293-APPsw cells	Oral	5–40 $\mu$ M	Resveratrol reduced A $\beta$ generation by inhibiting $\gamma$ -secretase	[72]
	In vitro: Formaldehyde-induced in N2a cells	Cell culture	0.1–10 $\mu$ M	1. Resveratrol reduced formaldehyde-induced neuronal damage; 2. Resveratrol reduced tau protein dephosphorylation through reducing GSK-3 $\beta$ activity	[73]
	In vivo: CdCl <sub>2</sub> -induced in male white albino Sprague Dawley rat	Oral	300 mg/kg	Resveratrol affected the PI3K/Akt/GSK-3 $\beta$ signaling pathway to improve tau hyperphosphorylation	[74]
	In vitro: HEK293- $\beta$ 2a; In vivo: Female wild type C57BL/6 mice	In vitro: Cell culture; In vivo: Intraperitoneal	In vitro: 100 $\mu$ M; In vivo: 25 mg/kg	Resveratrol could modulate PP2A, improving tau hyperphosphorylation	[75]
	In vitro: A $\beta$ (1–42)-induced in human neural stem cells; In vivo: A $\beta$ (1–42)-induced in male Kunming mice	In vitro: Cell culture; In vivo: Intracerebroventricular	In vitro: 10 $\mu$ M; In vivo: 0.02 and 0.2 mg/kg	1. Resveratrol restored GSH, GPX1, and HO-1 levels; 2. Resveratrol reduced inflammatory cytokines.	[76, 77]
	In vivo: Streptozotocin-induced in male Wistar rats; In vivo: Streptozotocin-induced in male Sprague-Dawley rats	Intraperitoneal; Oral	5 and 10 mg/kg; 50 and 75 mg/kg	Resveratrol treatment suppresses hippocampal AChE activity in rats with scopolamine-induced memory impairment	[78, 79]



AD mice, resulting in a reduction in inflammatory factors (TNF- $\alpha$ , IL-6, interleukin-1 $\beta$  [IL-1 $\beta$ ]) and an increase in superoxide dismutase (SOD) levels.<sup>43</sup>

In addition to its effects on oxidative stress and inflammation, Cur also inhibits AChE. Ahmed et al evaluated Cur's inhibitory effects on AChE in scopolamine-induced AD rats.<sup>44</sup> The inhibition of AChE increased with Cur doses ranging from 3 to 10 mg/kg. Another study found a similar dose-dependent inhibition of AChE in cadmium-induced AD rats, with Cur doses ranging from 12.5 to 25 mg/kg.<sup>45</sup> However, experiments from the same group revealed no significant difference in AChE inhibition with Cur doses between 25 and 50 mg/kg.<sup>46</sup>

## The Neuroprotective Effect of Quercetin on Alzheimer's Disease

QT has demonstrated significant neuroprotective effects against A $\beta$  aggregation. Treatment with QT in triple-transgenic AD (3xTg-AD) mice has been shown to reduce levels of A $\beta$ 1-40 and A $\beta$ 1-42, thereby improving cognitive function.<sup>47</sup> Moreover, preventive oral administration of QT (100 mg/kg) also decreased A $\beta$  levels in 3xTg-AD mice, mitigating cognitive decline.<sup>48</sup> Elfiky et al further discovered that QT may reduce A $\beta$  aggregation in aluminum chloride (AlCl<sub>3</sub>)-induced AD rats by upregulating the expression of ADAM10 and ADAM17 genes.<sup>49</sup>

Okadaic acid (OA) induces tau hyperphosphorylation in neuronal cells. Jiang et al created an in vitro AD model using HT22 cells and treated it with QT, demonstrating that QT significantly reduced OA-induced tau hyperphosphorylation.<sup>50</sup> This neuroprotective effect appears to be mediated through the PI3K/Akt/GSK3 $\beta$  signaling pathway.

In addition to its effects on A $\beta$  and tau, QT exerts neuroprotective benefits through its antioxidant and anti-inflammatory properties. An in vitro study showed that QT protected neurons from A $\beta$ -induced toxicity.<sup>51</sup> At higher concentrations (20 and 40  $\mu$ M), QT increased levels of 4-hydroxynonenal and 3-nitrotyrosine, indicating antioxidant activity, although this was not observed at lower concentrations (5 and 10  $\mu$ M). Interestingly, QT mitigated A $\beta$  neurotoxicity at both lower (5 and 10  $\mu$ M) and higher (20 and 40  $\mu$ M) concentrations, with no significant difference observed between the concentration groups. Cheng et al assessed the impact of QT on cognitive function in APP/PS1 mice, finding that QT improved cognitive abilities by increasing levels of glutathione (GSH), malondialdehyde (MDA), and SOD while decreasing ROS levels.<sup>52</sup> This neuroprotective effect appears to be linked to QT's activation of the Kelch-like ECH-associated protein 1 (Keap1)/nuclear factor erythroid 2-related factor (Nrf2)/Heme Oxygenase-1 (HO-1) pathway. Lasure et al observed elevated levels of the astrocyte marker GFAP in the brains of A $\beta$ 1-42-induced AD mice, suggesting the activation of inflammatory pathways within astrocytes, along with increased levels of pro-inflammatory cytokines.<sup>33</sup> QT treatment significantly reduced GFAP and pro-inflammatory cytokine levels in a dose-dependent manner within the 30–100 mg/kg range.

Additionally, QT has been shown to inhibit AChE activity. In cadmium-exposed rats, QT treatment at doses of 5, 25, and 50 mg/kg reduced AChE activity by 23%, 49%, and 54%, respectively.<sup>53</sup> Similarly, a 50 mg/kg dose of QT prevented the increase in AChE activity in the cortex and hippocampus induced by diabetes, leading to restored memory in diabetic rats.<sup>54</sup>

## The Neuroprotective Effect of Berberine on Alzheimer's Disease

BBR effectively reduces the production and accumulation of A $\beta$ , demonstrating significant neuroprotective effects. Previous studies have shown that BBR inhibits BACE1 activity, thereby reducing A $\beta$  production and accumulation.<sup>55</sup> Additionally, BBR enhances  $\alpha$ -secretase activity, further decreasing A $\beta$  levels in the hippocampus of AD mice. BBR has also been reported to activate autophagy through the class III PI3K/Beclin1 and AMPK/mTOR signaling pathways, promoting A $\beta$  clearance.<sup>57,58</sup> Notably, BBR improves cerebral vascular structure, function, and blood flow, facilitating the removal of A $\beta$  and other toxic substances, which ultimately enhances cognitive function in AD mice.<sup>82</sup> These findings confirm that BBR effectively reduces A $\beta$  formation and accumulation.

BBR has also been shown to alleviate tau hyperphosphorylation, although the precise mechanism remains unclear.<sup>26,83</sup> It has been observed that BBR reduces tau hyperphosphorylation by regulating the AKT/GSK-3 $\beta$  signaling pathway.<sup>59</sup> Other studies suggest that BBR mitigates tau hyperphosphorylation by enhancing PP2A activity and reducing GSK-3 $\beta$  activity.<sup>60,61</sup> Additionally, BBR promotes autophagy via the class III PI3K/Beclin1 pathway, facilitating tau clearance.<sup>59</sup> Collectively, BBR plays a pivotal role in mitigating tau hyperphosphorylation.

Due to its antioxidant and anti-inflammatory properties, BBR is a promising candidate for AD treatment. BBR has been shown to alleviate cellular oxidative stress by increasing brain levels of GSH and GSH peroxidase (GPX).<sup>62–64</sup> Further studies suggest that BBR exerts antioxidant effects by activating Nrf2, which regulates GSH, GPX4, and HO-1. Moreover, BBR inhibits the NF- $\kappa$ B signaling pathway in AD mice, reducing inflammatory cytokines such as IL-1 $\beta$ , TNF- $\alpha$ , and IL-6, thereby suppressing the inflammatory response and improving cognitive function.<sup>65</sup> Microglia, which play a role in the neuroinflammatory process associated with AD,<sup>84</sup> are also targeted by BBR, which inhibits their inflammatory response via the AMPK pathway.<sup>66</sup> While the exact mechanisms require further exploration, the antioxidant and anti-inflammatory effects of BBR are well established.

BBR has been shown to inhibit AChE activity, contributing to improved cognitive function and memory in AD.<sup>67</sup> In neuroblastoma cells (SH-SY5Y), BBR inhibited AChE activity.<sup>85</sup> In a sporadic AD mouse model induced by intracerebroventricular injection of streptozotocin, BBR inhibited AChE activity and improved spatial learning and memory.<sup>68</sup> Similarly, BBR reversed memory impairment in scopolamine-induced dementia mice by inhibiting AChE activity.<sup>69</sup> Overall, BBR is a valuable therapeutic agent for improving AD symptoms through the inhibition of AChE activity.

## The Neuroprotective Effect of Resveratrol on Alzheimer's Disease

Previous studies suggested that RES promotes A $\beta$  degradation not by directly affecting enzymes involved in A $\beta$  production and secretion, but rather through proteasome-mediated mechanisms that inhibit A $\beta$  generation.<sup>70</sup> However, subsequent research has indicated that RES can reduce A $\beta$  production by inhibiting BACE1.<sup>71</sup> Additionally, some studies propose that RES decreases A $\beta$  generation by inhibiting  $\gamma$ -secretase.<sup>72</sup> These conflicting findings may arise from variations in the cell types utilized.

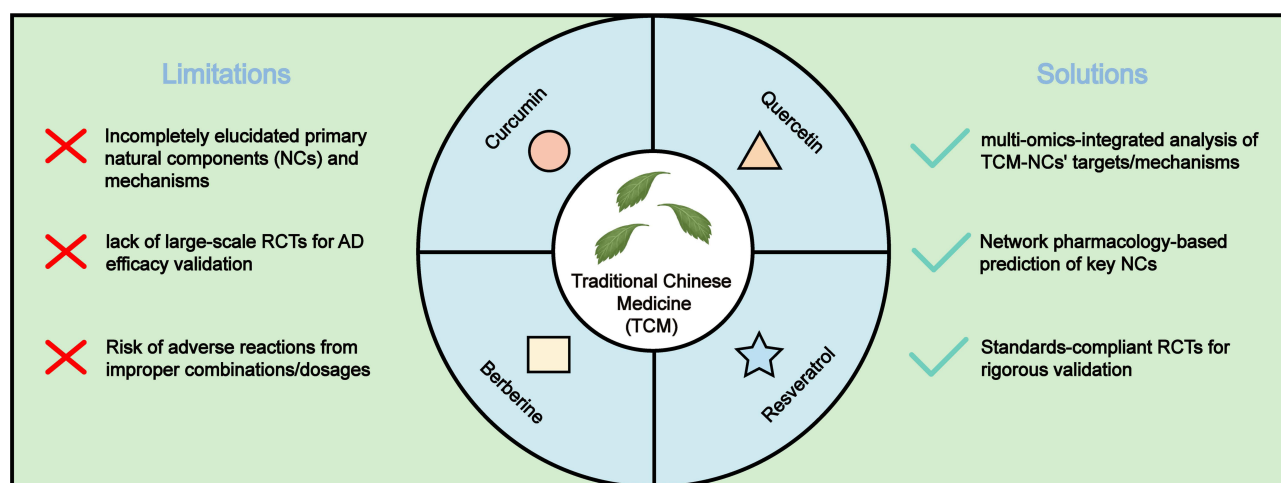
He et al were the first to demonstrate that RES mitigates formaldehyde-induced neuronal damage, potentially through tau protein dephosphorylation via reduced GSK-3 $\beta$  activity.<sup>73</sup> Shati et al explored whether RES modulates the PI3K/Akt/GSK-3 $\beta$  signaling pathway to alleviate tau hyperphosphorylation.<sup>74</sup> In vivo studies revealed that RES activates the PI3K/Akt/GSK-3 $\beta$  pathway and improves tau phosphorylation levels in AD rats. Given that protein phosphatase 2A (PP2A), a major tau phosphatase, shows reduced expression and activity in the brains of patients with AD, modulating PP2A activity may help alleviate tau hyperphosphorylation. Notably, RES has been shown to regulate PP2A, improving tau hyperphosphorylation and exerting neuroprotective effects.<sup>75</sup>

AMPK plays a pivotal role in the inflammatory and oxidative stress response. RES has been identified as an AMPK activator, suggesting its potential in mitigating neuroinflammation and oxidative damage. Chiang et al leveraged this property by treating A $\beta$ -induced oxidative stress and neuroinflammation in human neural stem cells (hNSCs) with RES.<sup>76</sup> Compared to controls, RES-treated hNSCs exhibited restored GSH, GPX1, and HO-1 levels, alongside a significant reduction in inflammatory cytokines (IL-1 $\beta$  and TNF- $\alpha$ ). Similar results were observed in an AD mouse model induced by intracerebroventricular injection of A $\beta$  and treated with RES.<sup>77</sup>

Furthermore, RES has been reported to inhibit AChE activity. Notably, multiple studies consistently show that RES treatment suppresses hippocampal AChE activity in rats with scopolamine-induced memory impairment.<sup>78,79</sup>

## Limitations and solutions of natural components of Traditional Chinese Medicine in treating Alzheimer's disease

Despite the promise of NDDS in enhancing the neuroprotective effects of TCM NCs, several challenges remain (Figure 2). First, the NCs of TCM are complex, and the primary active substances and mechanisms of action are not fully understood. Second, most NC formulations lack large-scale randomized controlled trials (RCTs) to validate their efficacy in AD treatment, necessitating improvements in clinical evidence. Lastly, improper combinations or dosages may lead to adverse drug reactions, such as the increased risk of hypoglycemic episodes when combining BBR with gliclazide.<sup>86</sup> To address these challenges, future research should systematically integrate multi-omics technologies, including transcriptomics, proteomics, and metabolomics, to thoroughly analyze the therapeutic targets and molecular mechanisms of TCM NCs. Network pharmacology approaches should be utilized to predict key active components. Building on these insights, rigorously designed RCTs must be conducted in strict adherence to drug development



**Figure 2** Limitations and solutions of natural components of Traditional Chinese Medicine in treating Alzheimer's disease.

standards. Moreover, a multidisciplinary evaluation system encompassing pharmacodynamics, safety, and clinical efficacy should be established, along with comprehensive risk assessment and management protocols. These measures will ensure the effectiveness and safety of TCM NCs in AD treatment, ultimately facilitating their clinical translation and application (Figure 2).

## Nanoparticle Drug Delivery Systems for Alzheimer's Disease

NDDS have garnered considerable attention for their potential to overcome the challenges associated with AD treatment, particularly in circumventing the BBB, which limits the penetration of most drugs into the brain. Efflux transporters, such as P-glycoprotein (P-gp), further restrict drug concentrations,<sup>87</sup> while traditional administration methods often result in suboptimal therapeutic effects and significant side effects.<sup>11,13</sup> NDDS present a promising solution by enhancing drug bioavailability, enabling targeted delivery, and minimizing toxicity. The brain-targeting delivery mechanisms of NPs primarily involve passive and active targeting strategies.<sup>88</sup> Passive targeting leverages the intrinsic physicochemical properties of NPs (eg, size, lipophilicity) and the physiological/pathological conditions of the BBB, allowing penetration through paracellular pathways (eg, tight junction disruption) or transcellular pathways (eg, passive diffusion). However, this approach often suffers from limited efficiency and specificity. In contrast, active targeting aims to deliver drugs specifically to target cells or tissues through mechanisms such as receptor-mediated transcytosis (RMT), adsorption-mediated transcytosis (AMT), and carrier-mediated transcytosis (CMT). RMT utilizes surface-modified ligands (eg, transferrin [TF]) that selectively bind to BBB endothelial cell receptors (eg, TF receptors), triggering endocytosis and transcytosis. AMT relies on electrostatic interactions between cationic carriers and negatively charged cellular membranes, promoting nonspecific endocytosis. CMT involves active internalization and intracellular delivery facilitated by functional carriers (eg, albumin), either naturally or through modification. In the realm of brain drug delivery, intranasal administration (nose-to-brain delivery) is a non-invasive method that bypasses the BBB via specialized pathways, including the olfactory and trigeminal nerve routes.<sup>89</sup> This approach minimizes systemic drug accumulation in non-target tissues while achieving precise delivery to cerebral tissues. The olfactory pathway involves passive diffusion of small molecules through the olfactory epithelium to the olfactory bulb, while macromolecules are absorbed via receptor-mediated endocytosis followed by axonal transport along olfactory nerve fibers to the CNS through olfactory cortical projections.<sup>90</sup> The trigeminal pathway involves drug absorption in the nasal respiratory region, with small molecules diffusing passively, and macromolecules entering trigeminal nerve terminals via receptor-mediated endocytosis, followed by bidirectional axoplasmic transport along trigeminal nerve axons to the CNS.<sup>91</sup> Additionally, NDDS enhance pharmacokinetics and pharmacodynamics by encapsulating drugs within nanoscale particles, offering benefits such as improved solubility, controlled release, and reduced off-target effects.<sup>16,92–94</sup> Among various NPs, polymeric, lipid-based, and protein-based NPs are particularly notable for their advantages, making them key subjects of research in AD

**Table 2** Application of Nanoparticle Drug Delivery System in Alzheimer's Disease

Nanoparticles		Drug	Experimental Model (in vitro / In vivo)	Route of Administration	Key Findings	References
Polymeric	PLGA	Donepezil	In vitro: HBMECs and HA (BBB); In vivo: A $\beta$ 25-35-induced in SD rats	In vitro: Cell culture; In vivo: Intravenous	1. More effective than donepezil in improving BBB permeability and disrupting the formation of A $\beta$ fibrils; 2. More effective than donepezil in exhibiting notable improvements in learning and memory capabilities	[95, 96]
		Memantine	In vivo: Scopolamine-induced in Swiss albino mice	Intrathecal	More effective than memantine in reducing A $\beta$ accumulation and neuronal damage in the brain	[97]
		Rivastigmine	In vivo: Scopolamine-induced in Wistar rats	-	More effective than rivastigmine in decreasing AChE activity in the brain	[98]
	CS	Galantamine	In vivo: Wistar rats	Intranasal	More effective than galantamine in decreasing protein levels and activity of AChE in the brain	[94]
		Rivastigmine	In vivo: AICl <sub>3</sub> -induced in albino rats	Intranasal	Intranasal administration is more effective than oral administration in histopathological results and the modulation of inflammatory pathway expression	[99]
	PM	Cyclosporine A	In vivo: LPS-induced in CD-1 mice	Intranasal	More effective than Cyclosporine A in anti-inflammatory effects through P-gp efflux inhibition	[100]

Lipid	Lip	Donepezil, memantine, and BACE-I siRNA	In vitro: Human astrocytes and HBEC-5i endothelial cells (BBB); In vivo: APP/PSI transgenic mice	In vitro: Cell culture; In vivo: Intranasal	1. More effective than free drug in exhibiting higher BBB permeability; 2. More effective than free drug in reducing Aβ deposition and suppressing pro-inflammatory cytokine expression	[101, 102]
		Rivastigmine	In vitro: SHSY5Y; In vivo: SD rats	In vitro: Cell culture; In vivo: Intranasal	More effective than intravenous administration in enhancing drug accumulation in the brain and inhibiting AChE activity	[103]
		Metformin	In vivo: STZ-induced in Wistar rats	Intravenous	More effective than metformin in reducing levels of hippocampal inflammatory cytokines (IL-1β, TNF-α, and TGF-β)	[104]
	SLN	EPO	In vivo: Aβ <sub>1-42</sub> -induced in Wistar rats	Intraperitoneal	More effective than free EPO in reducing Aβ deposition and alleviating oxidative stress	[105]
		MeHCl and TMPS	In vitro: murine BMVECs; In vivo: AICl <sub>3</sub> -induced in Wister Rats	In vitro: Cell culture; In vivo: Intraperitoneal	More effective than individual drugs in inhibiting Aβ deposition	[106]
		Rivastigmine	In vivo: BALB/c mice	Facial	Compared to intravenous administration, facial intradermal injection significantly enhanced drug accumulation in the brain	[107]
	NLC	Rivastigmine	In vitro: RPMI 2650 and AINI	Cell culture, intranasal	More effective than rivastigmine in improving brain-targeting efficiency and enabling controlled drug release	[108]
		Donepezil	In vivo: SD rats	Intranasal	1. More effective than Donepezil in enhancing drug utilization; 2. Intranasal administration achieved a brain drug concentration 9 folds higher than intravenous administration	[109]
	Protein	BSA	Tacrine	In vitro: sheep nasal mucosa	Tissue culture	Enhanced drug permeability and mucosal adhesion
HSA		Rivastigmine	-	-	More effective than rivastigmine in enhancing sustained drug release	[111]

therapy (Table 2). Overall, NDDS hold the potential to revolutionize the treatment of neurological disorders like AD by improving drug efficacy, safety, and targeted delivery.

## Polymeric Nanoparticles

Poly(lactic-co-glycolic acid) (PLGA), a widely studied copolymer composed of lactic acid (LA) and glycolic acid (GA), exhibits excellent drug release properties in the NP form.<sup>112</sup> By adjusting the LA/GA ratio, surface functionalization, and increasing the relative molecular weight of PLGA, improved drug release profiles can be achieved.<sup>112</sup> Additionally, PLGA boasts favorable biocompatibility, biodegradability, and non-immunogenicity, minimizing adverse drug reactions. Donepezil, an FDA-approved drug for treating AD, is typically administered orally for long-term therapy. However, oral administration often leads to gastrointestinal side effects, such as diarrhea and nausea.<sup>93</sup> To address this, researchers have developed donepezil-loaded PLGA NPs to reduce side effects while prolonging drug release and enhancing brain drug concentration. In vitro studies demonstrated that these NPs significantly improved BBB permeability and effectively disrupted A $\beta$  fibril formation.<sup>95</sup> In vivo experiments also showed notable improvements in learning and memory in rats treated with these NPs.<sup>96</sup> Encapsulation of donepezil in PLGA has been reported to reduce A $\beta$  accumulation and neuronal damage in mice, improving cognitive function.<sup>97</sup> Furthermore, PLGA NPs loaded with donepezil significantly reduced AChE activity in the brain compared to donepezil alone, reinforcing the potential of PLGA as an effective delivery system.<sup>98</sup>

Chitosan (CS), a naturally occurring polymer, is known for its low immunogenicity, biodegradability, and excellent biocompatibility.<sup>113</sup> Its unique adhesive properties and cationic nature enable strong interactions with negatively charged cell membranes, enhancing drug-targeting efficiency.<sup>114</sup> These properties also extend its retention time on the nasal mucosa, making it ideal for intranasal delivery to the brain.<sup>114</sup> Intranasal administration bypasses the BBB, avoids hepatic metabolism, minimizes systemic side effects, and provides rapid drug onset, making it an effective alternative drug delivery approach.<sup>115</sup> Galantamine, an FDA-approved reversible AChE inhibitor, modulates nicotinic receptors and inhibits A $\beta$  aggregation.<sup>116</sup> Despite its high bioavailability (90%–100%), oral and injectable formulations often cause gastrointestinal disturbances and muscle tremors. To mitigate these effects, Hanafy et al developed intranasal galantamine/CS composite NPs (CX-NP2).<sup>94</sup> Experimental results confirmed that CX-NP2 significantly reduced AChE protein levels and activity in rat brains without inducing toxicity, demonstrating both safety and efficacy. ElMosbah et al explored the therapeutic efficacy of oral versus intranasal administration of rivastigmine-loaded CS NPs.<sup>99</sup> Notably, intranasal delivery led to superior therapeutic outcomes, as evidenced by histopathological findings and modulation of inflammatory pathway expression.

Polymeric micelles (PMs) are self-assembled NPs composed of amphiphilic copolymers designed for optimal hydrophobicity/lipophilicity balance, NP size, drug loading efficiency, and stability in systemic circulation.<sup>117</sup> However, they are prone to premature drug release. To address this, researchers have employed stimuli-responsive strategies (eg, temperature, pH, and magnetic) to achieve controlled drug release.<sup>118</sup> Certain polymers, such as Pluronic and D- $\alpha$ -tocopheryl polyethylene glycol succinate (TPGS), can inhibit P-gp, enhancing intracellular drug accumulation by blocking efflux pumps and thereby improving therapeutic efficacy.<sup>119</sup> Guareschi et al developed cyclosporine A-loaded TPGS micelles for AD treatment, demonstrating that intranasal administration increased cyclosporine A concentrations in the brain and enhanced its anti-inflammatory effects, likely through P-gp efflux inhibition.<sup>100</sup>

## Lipid-Based Nanoparticles

Liposomes (Lips) are spherical vesicles composed of a phospholipid bilayer, typically ranging from 50 to 100 nm in size. They can encapsulate both hydrophilic and hydrophobic drugs, enhancing drug stability and extending circulation time.<sup>120</sup> Surface functionalization of Lips significantly improves drug solubility and bioavailability in brain regions, making them an effective tool for brain-targeted drug delivery. Lee et al utilized Lips to deliver donepezil, memantine, and BACE1 siRNA, evaluating their in vitro BBB penetration and therapeutic effects on AD.<sup>101</sup> The results demonstrated that Lip-encapsulated drugs exhibited significantly higher BBB permeability compared to free drugs, with a more pronounced reduction in A $\beta$  deposition and suppression of pro-inflammatory cytokine expression. These findings were further confirmed through in vivo experiments.<sup>102</sup> Notably, the surface charge of Lips can be easily modified, and both



cationic and anionic Lips offer distinct advantages for AD therapy.<sup>121</sup> Cationic Lips enhance cellular uptake through electrostatic interactions with the anionic surfaces of endothelial cell membranes. Yang et al engineered cationic cell-penetrating peptide (CPP)-modified rivastigmine Lips (CPP-Lp) for intranasal delivery.<sup>103</sup> In vitro BBB model evaluations demonstrated that CPP-Lp exhibited significantly greater BBB penetration efficiency compared to unmodified Lips. In vivo studies revealed that intranasal administration of these formulations substantially improved drug accumulation and retention in CNS regions, particularly the hippocampus and cerebral cortex, when compared to intravenous injection. Histopathological assessments confirmed minimal nasal mucosal irritation following CPP-Lp treatment. Remarkably, CPP-Lp administration resulted in sustained and potent inhibition of AChE activity, attributed to its prolonged release profile and enhanced tissue retention. In contrast, anionic Lips, such as phosphatidylserine (PS)-incorporated Lips, modulate microglial polarization by suppressing pro-inflammatory cytokines (eg, TNF- $\alpha$ , IL-6) and enhancing anti-inflammatory factors (eg, IL-10, TGF- $\beta$ ), thereby alleviating A $\beta$ -induced neuroinflammation.<sup>122</sup> Saffari et al successfully developed PS-based Lip NPs for metformin (MET) delivery (MET-PSL) in AD treatment.<sup>104</sup> Experimental results showed that, compared to free MET, the MET-PSL treatment group exhibited significantly reduced levels of hippocampal inflammatory cytokines (IL-1 $\beta$ , TNF- $\alpha$ , and TGF- $\beta$ ), confirming the pronounced anti-neuroinflammatory efficacy of this NDDS.

Solid lipid NPs (SLNs) are nano-carriers that utilize solid lipids as their core matrix. These NPs are considered safer than metal and polymer-based carriers due to the absence of organic solvents during the manufacturing process.<sup>123</sup> SLNs offer various advantages, including the ability to cross the BBB, high stability, high drug loading capacity, low toxicity, and controlled drug release.<sup>8</sup> In comparison to traditional Lips, which suffer from low drug loading capacity and short drug release times, SLNs offer significant advantages. Erythropoietin (EPO), known for its neuroprotective effects in AD, has shown promise in improving the pathological manifestations of the disease.<sup>124</sup> However, its poor ability to cross the BBB remains a major limitation. Dara et al addressed this by loading EPO into SLNs (EPO-SLN) for AD treatment.<sup>105</sup> The results demonstrated that EPO-SLN was more effective than free EPO in reducing A $\beta$  deposition and alleviating oxidative stress, providing enhanced neuroprotection. Another study utilized SLNs as carriers to co-load tramiprosate (TMPS, which inhibits A $\beta$  monomer oligomerization) and memantine hydrochloride (MeHCl), creating an M+T SLN drug delivery system to enhance neuroprotective effects.<sup>106</sup> Both in vitro and in vivo studies showed that M+T SLNs outperformed individual drugs in inhibiting A $\beta$  deposition. In addition to intranasal administration, the facial trigeminal nerve pathway has emerged as an effective route for brain drug delivery. Permana et al developed a thermosensitive gel loaded with rivastigmine SLNs, which was delivered to the brain via facial intradermal injection.<sup>107</sup> Compared to intravenous administration, facial intradermal injection significantly enhanced drug accumulation in the brain.

Nanostructured lipid carriers (NLCs), considered a new generation of SLNs, are composed of a blend of solid and liquid lipids.<sup>125</sup> NLCs aim to address some limitations of SLNs, such as enhancing drug loading capacity and preventing drug release during storage.<sup>125</sup> Cunha et al developed a thermosensitive in situ nasal gel based on NLCs loaded with rivastigmine (G-RVG-NLC).<sup>108</sup> Compared to free rivastigmine, G-RVG-NLC demonstrated significantly enhanced delivery efficiency. Studies showed that G-RVG-NLC not only prolonged drug retention time on the nasal mucosa but also facilitated controlled drug release via its thermosensitive properties, significantly improving brain-targeting efficiency through intranasal administration. This approach offers a highly effective nasal delivery strategy for AD treatment. Another study evaluated the brain delivery efficiency of donepezil-loaded NLCs (DNZ NLCs).<sup>109</sup> The results revealed that DNZ NLCs significantly enhanced drug utilization compared to free DNZ, with intranasal administration achieving brain drug concentrations nine times higher than intravenous administration, further underscoring the superiority of intranasal delivery for brain-targeted drug delivery.

## Protein-Based Nanoparticles

Serum albumin, the most abundant functional protein in human plasma, has emerged as one of the most clinically translatable NCs for neurological disorders. Its unique molecular structure enables efficient binding of both lipophilic and hydrophilic drugs, while its low immunogenicity, biodegradability, and excellent biocompatibility make it an attractive option.<sup>126</sup> Among various albumin variants, bovine serum albumin (BSA) and human serum albumin (HSA) are the most widely utilized protein-based drug delivery platforms. In a pioneering study, Luppi et al systematically characterized

tacrine-loaded BSA NPs, demonstrating favorable physicochemical properties for drug delivery: the NCs exhibited a monodisperse size distribution (mean diameter <300 nm) and a negative surface charge, which collectively enhanced drug permeation across biological barriers and provided remarkable mucoadhesive properties.<sup>110</sup> These findings strongly support the potential application of BSA-based NPs in intranasal delivery systems for targeted AD therapy. In another study, Avachat et al developed HSA NPs loaded with RT to enhance sustained drug release.<sup>111</sup> In vitro evaluations revealed significantly modulated release kinetics: free RT exhibited rapid release (86% within 5 hours), whereas the HSA-based formulation achieved a prolonged release (53.93% over 12 hours), highlighting its potential for controlled drug delivery. From a clinical translation and safety perspective, HSA demonstrates superior potential as a drug carrier compared to other alternatives, due to its low immunogenicity and established regulatory approval history, as evidenced by FDA-approved HSA-based therapeutics such as Abraxane (paclitaxel-bound albumin NPs) for cancer treatment.<sup>127</sup> These findings underscore the significant potential of HSA as a nanocarrier platform for AD therapy.

Advantages and Limitations of Different Delivery Systems

Numerous NPs have been successfully developed, with polymeric NPs, lipid-based NPs, and protein-based NPs emerging as the three primary delivery systems (Figure 3). Polymeric NPs offer distinct advantages, including controlled release and a broad drug-loading capacity for various therapeutic agents. However, unmodified polymeric NPs exhibit limited BBB permeability, requiring surface functionalization to enhance penetration efficiency. Additionally, degradation byproducts, such as LA from PLGA, may disrupt the delicate brain microenvironment. Lipid-based NPs exhibit excellent biocompatibility due to their biomimetic phospholipid bilayer structure, making them especially effective for delivering lipophilic compounds and nucleic acids. Despite their advantages, these systems face challenges such as rapid clearance by serum proteins, which can be mitigated by PEGylation to extend circulation time,<sup>128</sup> suboptimal targeting specificity relying mainly on passive accumulation,<sup>103</sup> and limited loading efficiency for hydrophilic drugs. Protein-based NPs possess unique endogenous BBB transport capabilities, mediated through gp60 receptors and SPARC (secreted protein acidic and rich in cysteine)-facilitated pathways.<sup>129</sup> Their inherent antioxidative and anti-inflammatory properties offer additional therapeutic benefits for neurodegenerative disorders. However, the high production costs of materials like HSA limit their applicability, and current formulations are mainly restricted to hydrophobic small molecules, presenting difficulties in delivering nucleic acids or large protein-based therapeutics.

As research progresses, single-component nanomaterials are proving insufficient to meet the complex therapeutic needs of various diseases. The synergistic integration of multiple nanomaterials into composite NPs is expected to offer a more efficient drug delivery solution. Additionally, the safety profile of nanomedicines remains a critical concern. Encapsulating drugs within biomimetic nanomaterials may significantly enhance their biocompatibility and safety,




Different delivery systems	 Polymeric nanoparticles	 Lipid-based nanoparticles	 Protein-based nanoparticles
Advantages	<div>✓ Controlled release</div> <div>✓ Broad drug-loading capacity</div>	<div>✓ Exceptional biocompatibility from their biomimetic phospholipid bilayer structure</div> <div>✓ Optimized lipophilic/nucleic acid delivery</div>	<div>✓ Unique endogenous BBB-transport capabilities</div> <div>✓ Inherent dual antioxidative/anti-inflammatory neuroprotection</div>
Limitations	<div>✗ Brain microenvironment perturbation by PLGA degradation byproducts</div> <div>✗ Native BBB-penetration deficiency demanding surface functionalization</div>	<div>✗ Rapid clearance by serum proteins</div> <div>✗ Suboptimal targeting specificity</div> <div>✗ Limited hydrophilic-drug loading capacity</div>	<div>✗ High production costs</div> <div>✗ Hydrophobic-small-molecule-restricted formulations</div>

Figure 3 Advantages and limitations of different delivery systems.



potentially mitigating some of the current challenges. These innovative approaches open new frontiers for future research, with the potential to drive significant advancements in the field of nanomedicine.

## The potential application of Natural components of Traditional Chinese Medicine delivery via nanoparticle drug delivery systems in the treatment of Alzheimer's disease

As discussed earlier, NCs of TCM exhibit various neuroprotective effects, making them promising therapeutic agents for AD.<sup>130</sup> However, their low bioavailability and limited BBB penetration have hindered their therapeutic potential and clinical application.<sup>131</sup> NDDS can overcome these limitations by encapsulating NCs of TCM in NPs, improving their bioavailability and targeting them to the brain. NDDS also allow for prolonged release, reducing dosing frequency and enhancing patient compliance. Thus, the delivery of NCs of TCM via NDDS represents a promising and feasible approach for AD treatment. The following section discusses several NCs of TCM that have been studied in delivery via NDDS for AD treatment and research. This section summarizes their therapeutic effects, mechanisms of action, the structure of NPs used for drug loading, and their delivery mechanisms ([Supplementary Tables 1–4](#)).

### Curcumin

#### Curcumin Delivery via Polymeric Nanoparticles for the Treatment of Alzheimer's Disease

Over a decade ago, Mathew et al successfully using a single emulsion solvent evaporation method and synthesized Cur-PLGA NPs by encapsulating Cur in PLGA.<sup>132</sup> These NPs maintained the physicochemical properties of Cur while demonstrating good water solubility. In vitro studies indicated that this formulation could inhibit A $\beta$  aggregation, exhibiting potential anti-AD effects. In another study, the team conjugated an anti-A $\beta$  protein aptamer (NN2) to the Cur-PLGA NPs to further reduce A $\beta$  aggregation.<sup>133</sup> Additionally, the Tet-1 peptide, which specifically targets neurons and facilitates retrograde delivery within neuronal cells, was combined with Cur-PLGA NPs (Tet-Cur-PLGA). This formulation demonstrated anti-A $\beta$  and antioxidant properties in vitro.<sup>134</sup> Interestingly, Tet-Cur-PLGA was more effective than Cur-PLGA in inhibiting A $\beta$  aggregation, while showing comparable antioxidant activity to Cur-PLGA. Although these NP formulations hold promise for AD treatment, in vivo validation is still pending. Fan et al conjugated the B6 peptide, a brain-targeting peptide, to Cur-loaded NPs (PLGA-PEG-B6/Cur) for testing in transgenic mice.<sup>135</sup> They found that PLGA-PEG-B6/Cur significantly enhanced the spatial learning abilities and memory function of the mice. Furthermore, it reduced A $\beta$  formation and deposition, and decreased tau protein phosphorylation levels. In another study, researchers enhanced the targeting capability of Cur-PLGA NPs by modifying their surface with a glycopeptide (g7) capable of crossing the BBB. In vitro studies demonstrated that Cur-PLGA-g7 was more effective than Cur-PLGA in reducing A $\beta$  aggregation.<sup>136</sup> Huang et al developed a novel NP formulation, CRT-PLGA-S1-Cur, to improve AD treatment.<sup>137</sup> This formulation combines PLGA loaded with Cur and the S1 peptide, an A $\beta$  generation inhibitor, and is further modified with the brain-targeting peptide CRT, which targets the TF receptor to enhance BBB permeability. The results indicated that CRT-PLGA-S1-Cur exhibited the most significant improvement in transgenic AD mice compared to other treatment groups, including Cur alone, PLGA-Cur, and PLGA-S1-Cur. Additionally, CRT-PLGA-S1-Cur significantly reduced levels of A $\beta$ , oxidative stress, and inflammatory factors in the brains of AD mice. Similar findings were reported in another study using this NP formulation.<sup>138</sup> Huo et al reported that Cur-loaded selenium-PLGA (Cur/Se-PLGA) nanospheres enhanced BBB penetration, attributed to the presence of selenium NPs.<sup>139</sup> These nanospheres significantly reduced A $\beta$  aggregation and decreased inflammation in AD mice compared to Cur and Cur-PLGA. Doggui found that PLGA synthesized with a GA to LA ratio of 65:35 (Cur-PLGA 65:35) exhibited small size and high encapsulation efficiency.<sup>140</sup> In vitro studies demonstrated that Cur-PLGA 65:35 protected SK-N-SH cells from H2O<sub>2</sub>-induced damage by inducing Nrf2 expression. Djioke Paka et al emphasized the importance of controlling drug release capacity as a critical parameter for enhancing nano-delivery efficiency. By adjusting the ratio of GA to LA to 50:50, they improved the overall efficiency of the drug delivery system.<sup>141</sup> Research showed that Cur-PLGA 50:50 released Cur at a faster rate compared to Cur-PLGA 65:35. Moreover, Cur-PLGA 50:50 demonstrated superior anti-inflammatory and antioxidant activities compared to free Cur. The Wnt/ $\beta$ -catenin pathway plays a critical role not only in regulating A $\beta$

levels but also in neuronal development, differentiation, and self-renewal. Targeting this pathway has thus emerged as a promising strategy for AD treatment. Tiwari et al observed that Cur-PLGA NPs mitigated the toxic effects of A $\beta$  on neurogenesis in AD mice and enhanced the brain's self-repair mechanisms, likely due to Cur's activation of the Wnt/ $\beta$ -catenin pathway.<sup>142</sup> This approach proved to be more effective than Cur alone. Sublingual administration is an effective strategy for enhancing patient compliance and reducing dosing frequency compared to oral administration. Yekeler et al pioneered the use of 3D printing to embed Cur-loaded PLGA NPs into a sodium alginate/gelatin matrix.<sup>143</sup> This matrix dissolves rapidly in artificial saliva (dissolution time of 2.3 seconds), enabling sublingual drug delivery. In vitro studies suggest that Cur may exert neuroprotective effects in AD treatment by modulating the Wnt/ $\beta$ -catenin and PI3K/Akt/GSK-3 $\beta$  pathways. Therefore, further validation of the feasibility and safety of this NP-based drug is required through in vivo animal studies and clinical trials. Lin et al proposed a thermosensitive hydrogel delivery system using PLGA-PEG-PLGA loaded with Cur (PGC) to prevent the progression of AD.<sup>144</sup> Their study indicated that PGC reduced cell toxicity and oxidative stress in N2a cells induced by AlCl<sub>3</sub>, while also suppressing inflammation in BV2 cells. Further research revealed that weekly intramuscular injections of PGC in an AD rat model effectively improved cognitive function and prevented disease progression. Additionally, PGC can transition from a solution to a gel at 37°C, allowing for controlled, sustained release of Cur.

### Curcumin Delivery via Lipid-Based NPs for the Treatment of Alzheimer's Disease

Kakkar et al developed Cur-loaded SLNs (Cur-SLNs) and validated their oral bioavailability in rats.<sup>145</sup> Compared to free Cur (50 mg/kg), the oral bioavailability of Cur-SLNs at varying dosages was found to be 155 times higher (1 mg/kg), 59 times higher (12.5 mg/kg), 32 times higher (25 mg/kg), and 39 times higher (50 mg/kg). Notably, Cur-SLNs can be stored for up to 12 months at 2–8°C without any loss of drug potency. Aluminum deposition in the brain is a contributing factor to AD pathology, as it induces neurotoxicity that leads to A $\beta$  deposition, tau phosphorylation, and neuronal loss.<sup>17</sup> In previous studies, the same research team evaluated the efficacy of Cur-SLNs in orally administered AlCl<sub>3</sub>-induced AD mice.<sup>146</sup> The results indicated that Cur-SLNs were more effective in improving the learning and cognitive abilities of the mice. AChE activity in the mouse brains showed that the 50 mg/kg dose of Cur-SLNs achieved significantly better results, with a 73% inhibition rate of AChE activity, compared to only 22% inhibition with Cur alone. Furthermore, histological examination of the mouse brain tissue revealed that the cellular composition and structure were more intact after treatment with Cur-SLNs than with Cur, even at lower doses. Tissue transglutaminase (TG2) is a multifunctional protein that promotes the formation of amyloid aggregates in AD pathology.<sup>147</sup> Recent studies have shown that Cur can exert neuroprotective effects in AD mice by modulating TG2 expression. However, the low bioavailability of Cur limits its in vivo application. Campisi et al utilized SLNs as a carrier to deliver Cur (Cur-SLN) for the treatment of AD mice.<sup>148</sup> This study provided the first evidence that Cur-SLNs can modulate TG2 expression in vivo, significantly enhancing the concentration of Cur and improving cognitive abilities and memory function in AD mice. In summary, SLN-based Cur delivery represents an effective pharmaceutical formulation for AD treatment.

NLCs address the limitations of SLNs, enhancing the bioavailability of Cur in vivo. Malvajerd et al developed two types of nanomedicines: Cur-SLNs and Cur-NLCs, aimed at optimizing lipid NP preparations and selecting a more suitable drug carrier.<sup>149</sup> Experimental results demonstrated that both Cur-SLNs and Cur-NLCs increased Cur absorption in the brain compared to free Cur. Notably, Cur-NLCs facilitated over four times greater brain absorption than Cur-SLNs. In terms of drug encapsulation efficiency, Cur-SLNs achieved  $82 \pm 0.49\%$ , while Cur-NLCs reached  $94 \pm 0.74\%$ . These findings suggest that Cur-NLCs may be a superior option for AD treatment. Building on these findings, the same authors applied Cur-loaded NLCs (Cur-NLCs) in an A $\beta$ -induced rat model of AD.<sup>92</sup> In vivo results confirmed that Cur-NLCs significantly enhanced Cur accumulation in the brain and serum levels in the rats. Interestingly, both pre-treatment and treatment groups were evaluated for neuroprotective effects. The pre-treatment group showed superior neuroprotection against AD, likely due to the creation of a more favorable environment for maintaining neuronal function, thus reducing damage from A $\beta$  and reactive oxygen species (ROS). These findings highlight the potential of Cur-NLCs in AD treatment and provide a basis for further research into their prevention and management. To optimize Cur-NLCs for higher drug encapsulation, prolonged release, and enhanced stability, Agrawal et al employed an enhanced melt-emulsification-ultrasonication method to prepare drug-loaded NLCs.<sup>150</sup> They used the Box-Behnken design for

experimental design and optimization. The optimized formulation yielded a material ratio of 3.092, a surfactant concentration of 2.131%, and an ultrasonication time of 4.757 minutes. The resulting NPs had a size of  $121.8 \pm 55.81$  nm and exhibited a spherical and uniform shape, with an encapsulation efficiency of  $93.62 \pm 0.68\%$  and a drug release rate of  $92.73 \pm 0.06\%$ . Notably, Cur-NLCs demonstrated an initial burst release followed by sustained release over 48 hours. These results meet the criteria for brain delivery and support further development of Cur-NLCs as a therapeutic option for AD.

### Curcumin Delivery via Protein-Based NPs for the Treatment of Alzheimer's Disease

To enhance A $\beta$  clearance efficiency and improve Cur's ability to cross the BBB, Yang et al utilized electrostatic interactions to conjugate positively charged CS with negatively charged BSA, forming NPs loaded with Cur (CS-BSA@Cur).<sup>151</sup> In an in vitro BBB model, the permeability of CS-BSA@Cur at 1, 2, and 3 hours was 37.7%, 45.6%, and 60.2%, respectively, compared to free Cur, which exhibited only 12.3% permeability at 1 hour, 20.3% at 2 hours, and 29.8% at 3 hours. These results demonstrate that CS-BSA@Cur significantly improves the bioavailability of Cur. The enhanced permeability is facilitated through vesicular and micellar transport mechanisms. Notably, CS-BSA@Cur also better activates microglia, accelerating A $\beta$  clearance and providing neuroprotective effects compared to Cur alone. In summary, CS-BSA@Cur shows considerable potential in enhancing AD treatment.

## Quercetin

### Quercetin Delivery via Polymeric Nanoparticles for the Treatment of Alzheimer's Disease

PLGA, known for its excellent biocompatibility, is widely used as a drug delivery vehicle. In this regard, Sun et al developed PLGA-encapsulated QT (PLGA@QT) to inhibit and degrade A $\beta$ 42 fibrils, assessing its therapeutic effects on AD.<sup>152</sup> In vitro studies demonstrated that PLGA@QT could suppress A $\beta$ 42 aggregation induced by excess metal ions, thereby reducing neuronal cell damage. Additionally, in vitro toxicity tests revealed low cytotoxicity, and further in vivo studies showed no pathological abnormalities in various organs, including the heart, liver, spleen, lungs, and kidneys, confirming the safety of PLGA@QT. Behavioral experiments indicated that PLGA@QT significantly improved cognitive and memory functions in AD mice, outperforming the QT group. Collectively, these findings provide strong evidence for the potential of PLGA@QT in AD treatment.

### Quercetin Delivery via Lipid-Based Nanoparticles for the Treatment of Alzheimer's Disease

A study prepared QT-loaded Lips (QT Lips) as a delivery system and enhanced cognitive function in AD animals through nasal administration.<sup>153</sup> The results demonstrated that QT Lips significantly improved cognitive performance in AD rats compared to free QT. Histological analysis showed that QT Lip treatment alleviated the reduction in hippocampal and cholinergic neuron densities in AD rats.

In a related study, QT-loaded SLNs (SLN-QT) improved cognitive impairment and spatial learning abilities in A $\beta$ 1-3-induced AD mice.<sup>154</sup> The study also found that SLN-QT maintained levels of GSH and nitrite in the brain, suggesting that SLN-QT can effectively target the CNS for AD treatment. Similarly, Rishitha et al investigated the therapeutic effects of SLN-QT in a pentylenetetrazol (PTZ)-induced AD zebrafish model.<sup>155</sup> The results indicated that SLN-QT reduced learning and memory impairments caused by PTZ in the hippocampus. The primary mechanisms included an increase in reduced GSH levels and a decrease in thiobarbituric acid-reactive substances and AChE levels. Furthermore, no significant difference in therapeutic effects was observed between SLN-QT and donepezil at the same dosage, highlighting its effective neuroprotective properties. NLCs represent a new generation of nano-lipid delivery systems that overcome the limitations of SLNs. Patil et al utilized NLCs to deliver QT (NLC-QT) via intranasal administration, enhancing the drug's targeting capability.<sup>156</sup> Research indicated that NLC-QT did not damage the nasal mucosa during delivery and achieved a higher brain concentration compared to free QT. Additionally, NLC-QT demonstrated sustained release properties, maintaining drug release over 24 hours. To further optimize NLC-QT, Sonawane et al employed methods such as melt emulsification-high-pressure homogenization and a Box-Behnken design to prepare an in situ gel of NLC-QT.<sup>157</sup> Results showed that the nasal mucosal permeability of the NLC-QT in situ gel was three times greater than that of free QT. Notably, pharmacokinetic data confirmed that the targeting efficiency of intranasal administration of

NLC-QT in situ gel was 117.47% compared to free QT. Further studies revealed that NLC-QT in situ gel exhibited superior therapeutic effects compared to donepezil, underscoring the significant potential of NLCs as a delivery carrier for QT in AD treatment. To evaluate and improve lipid NCs, Aditya et al conducted a comparative study between NLCs and SLNs.<sup>158</sup> The results showed that NLCs loaded with QT (NLC-QT) exhibited smaller particle size, higher drug loading capacity, and enhanced bioavailability compared to SLN-QT. Kumar et al also compared NLCs and SLNs to assess their performance as drug delivery systems for QT.<sup>159</sup> In vitro studies demonstrated that both NLC-QT and SLN-QT effectively penetrated Caco-2 cells. Further in vivo research indicated that both NLC-QT and SLN-QT had better bioavailability compared to free QT, with enhancements of 5.4-fold and 3.5-fold, respectively. Additionally, the drug clearance time was significantly prolonged, by 5.8-fold for NLC and 3.5-fold for SLN. These findings highlight that both NLCs and SLNs can significantly enhance the therapeutic efficacy of QT. In an A $\beta$ 13-induced rat model, administration of NLC-QT and SLN-QT significantly reduced the decline in GSH levels, with NLC-QT showing a more pronounced effect. Pinheiro et al further enhanced the ability of NPs to cross the BBB by modifying NLCs loaded with QT (RVG29-NLC-QT) and SLNs loaded with QT (RVG29-SLN-QT) using RVG29, a peptide that targets nicotinic ACh receptors (nAChR) and facilitates binding to neuronal cells and the BBB.<sup>160</sup> The results indicated that the modified NPs (RVG29-NLC-QT and RVG29-SLN-QT) exhibited 1.5 times greater BBB penetration compared to their unmodified counterparts (NLC-QT and SLN-QT). Furthermore, both RVG29-modified NPs demonstrated enhanced inhibition of A $\beta$  aggregation. In another study, TF was used to modify NLC-QT (TF-NLC-QT) and SLN-QT (TF-SLN-QT) to improve their BBB-crossing ability and A $\beta$  aggregation inhibition.<sup>161</sup> However, the permeability of TF-modified NPs (TF-NLC-QT and TF-SLN-QT) did not show a significant increase, likely due to the saturation of endogenous TF transport, which hindered receptor-mediated active transport of the TF-modified NPs.

### Quercetin Delivery via Protein-Based Nanoparticles for the Treatment of Alzheimer's Disease

Dou et al developed novel albumin-based NPs by encapsulating QT within HSA to form HSA@QT NPs (HQ NPs) for potential therapeutic use in advanced AD.<sup>162</sup> The HQ NPs exhibited significant antioxidant activity, effectively protecting PC12 cells from H<sub>2</sub>O<sub>2</sub>-induced oxidative damage. When administered intranasally to 11-month-old APP/PS1 mice—an established model for advanced AD—these NPs demonstrated multiple therapeutic benefits: prevention of body weight loss, improved survival rates, and substantial reduction in key pathological features, including oxidative stress, neuronal apoptosis, A $\beta$  aggregation, and synaptic dysfunction in brain tissues. Notably, administration of HQ NPs led to a significant recovery of severely impaired cognitive function. In addition to their potent anti-AD effects, HQ NPs exhibited excellent biosafety and biocompatibility due to their natural composition. While this study confirmed the neuroprotective effects of HQ NPs, a comprehensive comparative analysis of their therapeutic efficacy against QT is still required and merits further exploration.

## Berberine

### Berberine Delivery via Polymeric Nanoparticles for the Treatment of Alzheimer's Disease

Saleh et al investigated whether Tet-modified PLGA NPs loaded with BBR (BBR/PLGA-Tet) could enhance the bioavailability and therapeutic efficacy of BBR.<sup>163</sup> The results demonstrated that, compared to BBR alone, the BBR/PLGA-Tet treatment group showed significantly reduced levels of A $\beta$ 42 and phosphorylated tau protein, alongside notable improvements in neuroplasticity and cognitive function in rats. These findings indicate that BBR/PLGA-Tet enhances both the bioavailability and therapeutic effects of BBR. Another study reported that CS BBR NPs (BBR-NPs) effectively alleviated scopolamine-induced cognitive impairment.<sup>164</sup> Specifically, BBR-NPs exhibited superior inhibition of AChE, reduced A $\beta$ 42 and tau protein levels, and demonstrated stronger anti-inflammatory and antioxidant properties than BBR or donepezil. Notably, BBR-NPs (7 mg/kg) significantly improved learning and memory in AD rats, requiring only one-sixth of the recommended BBR dose (50 mg/kg).

### Berberine Delivery via Lipid-Based Nanoparticles for the Treatment of Alzheimer's Disease

Recent research has shown that lactoferrin (Lf)-modified polyethylene glycol (PEG)ylated BBR Lips (BR-Lf) can enhance the anti-AD effects of BBR.<sup>16</sup> Both modified and unmodified Lf NP groups exhibited superior neuroprotective



effects compared to free BBR. Notably, the BR-Lf group demonstrated the most significant improvement in behavioral performance relative to the unmodified Lf groups, likely due to the presence of Lf receptors (LfRs) on the BBB endothelial cells, which facilitated increased brain targeting of the NPs.<sup>165</sup> Additionally, PEGylation extended the in vivo circulation time of BBR-loaded nanoLips, significantly reducing the clearance rate of BBR in plasma and tissues. These findings suggest that BR-Lf may hold promise as a potential therapeutic agent for AD. However, further investigation is required to assess the dose-dependent effects of BR-Lf's neuroprotective role and to determine the optimal administration method. The use of imidacloprid has been linked to potential irreversible harm, particularly neurotoxicity. In a study by El Gazzar et al, the neuroprotective effects of BBR-loaded PEGylated nanoLips (Ber-Lip) against imidacloprid-induced neuronal damage were explored.<sup>166</sup> Experimental results revealed that Ber-Lip significantly alleviated neuronal injury caused by imidacloprid exposure, primarily by inhibiting NOD-like receptor protein 3 (NLRP3)/Caspase-1/gasdermin D (GSDMD)-mediated pyroptosis.

To address the challenges of poor oral bioavailability associated with BBR, SLNs have emerged as a promising delivery strategy. In a recent study, Nguyen et al developed BBR-SLNs using stearic acid (SA), glyceryl monostearate (GMS), and Poloxamer 407 (P407).<sup>167</sup> Through systematic optimization, a formulation with a weight ratio of 1:9:2 (SA:GMS: P407) exhibited optimal physicochemical properties. Additionally, BBR-SLNs produced via spray drying showed enhanced stability and sustained release characteristics compared to their suspended counterparts, likely due to the solid-state form of SLNs improving their physicochemical attributes. These results suggest that spray-dried SLNs could be an effective delivery method for expanding BBR's therapeutic potential in AD. BBR-loaded NLCs (Berb-NLC) have been developed for their therapeutic potential in A $\beta$ 13-induced AD rat models.<sup>17</sup> Experimental data demonstrated notable improvements in cognitive function and spatial learning in AD rats following Berb-NLC treatment. A comparative therapeutic evaluation showed superior efficacy of oral Berb-NLCs over conventional treatments, including free BBR and donepezil, indicating successful overcoming of BBR's bioavailability limitations. Controlled release analysis revealed that Berb-NLCs achieved approximately 80% drug release within 24 hours, confirming the system's sustained-release properties. While these findings position Berb-NLCs as a promising alternative for AD treatment, the study did not assess cerebral distribution patterns, a critical area for future research. Intranasal delivery has gained attention as a promising approach for CNS disorders, due to its ability to bypass the BBB and provide direct drug delivery to the brain. Abo El-Enin et al pioneered the design of CS-coated BBR-loaded NLCs (BER-CTS-NLCs) and evaluated their efficacy through intranasal administration.<sup>168</sup> Pharmacokinetic profiling and brain-targeting assessments revealed significantly higher cerebral drug concentrations and improved brain-to-blood area under the curve (AUC) ratios in AD rats treated with BER-CTS-NLCs compared to conventional BBR administration. Additionally, BER-CTS-NLCs exhibited prolonged drug release and enhanced drug penetration into the nasal mucosa. Histological evaluations confirmed the excellent biocompatibility of BER-CTS-NLCs, with no mucosal damage, establishing their safety for intranasal applications. Collectively, these findings suggest that intranasal BER-CTS-NLCs could enhance therapeutic outcomes in neurodegenerative diseases, particularly AD. However, clinical data is essential to evaluate the efficacy and risk/benefit ratio of BER-CTS-NLCs in human subjects.

### **Berberine Delivery via Protein-Based Nanoparticles for the Treatment of Alzheimer's Disease**

Zhang et al successfully developed BBR NPs based on HSA (BBR-HSA) through spontaneous electrostatic interactions.<sup>169</sup> Comprehensive characterization revealed that the NPs exhibited excellent physicochemical properties: uniform spherical morphology with an average diameter of approximately 100 nm, a drug loading capacity of 19.37%, encapsulation efficiency of 70.34%, and a production yield of 88.91%. In vitro release studies showed that free BBR released rapidly within 24 hours, while BBR-HSA exhibited significantly sustained release over the same period. In an AD cellular model, both BBR and BBR-HSA provided significant protection against H<sub>2</sub>O<sub>2</sub>-induced oxidative damage, as indicated by enhanced catalase (CAT) activity. Notably, BBR-HSA demonstrated superior antioxidative protection compared to free BBR. These findings support the potential application of natural product-based nanodelivery systems (NDDS) in AD treatment, positioning BBR-HSA as a promising therapeutic strategy for oxidative stress-related neurodegenerative disorders.

## Resveratrol

### Resveratrol Delivery via Polymeric Nanoparticles for the Treatment of Alzheimer's Disease

Emerging evidence underscores the substantial impact of glucolipid metabolic disorders on cognitive function, particularly through insulin resistance mechanisms that exacerbate A $\beta$  aggregation and tau protein hyperphosphorylation.<sup>170</sup> Additionally, growing research identifies the gut microbiota as a critical regulator of glucolipid homeostasis.<sup>171</sup> To address both microbial dysbiosis and metabolic dysfunction in AD pathology, Yang's team engineered a novel flower-like nanoplatfrom: RES-loaded selenium NPs/CS NPs (Res@SeNPs@Res-CS-NPs).<sup>172</sup> Experimental validation demonstrated that this nanoconstruct alleviated cognitive deficits in AD models through several mechanisms, including gut microbiota restoration, oxidative stress reduction, neuroinflammation suppression, and regulation of glucolipid metabolism. However, a direct comparison of therapeutic efficacy between Res@SeNPs@Res-CS-NPs and RES has not been explored in current research. In a subsequent study, the team developed an advanced nanodelivery system by using ionic crosslinking of CS with sodium tripolyphosphate (TPP) for RES encapsulation (Res-CS/TPP-NPs).<sup>173</sup> To enhance BBB penetration, they created a targeted delivery system by conjugating a brain-targeting peptide (TG: TGNKALHPHNG) to the NP surface, resulting in TG-Res-CS/TPP-NPs. Studies revealed that this targeted formulation effectively mitigated lipid accumulation-induced insulin resistance and modulated AD-related pathological markers (A $\beta$  plaque formation and tau protein hyperphosphorylation) via the JNK/AKT/GSK3 $\beta$  signaling pathway. Moreover, TG-Res-CS/TPP-NPs demonstrated superior therapeutic outcomes compared to RES and Res-CS/TPP-NPs.

### Resveratrol Delivery via Lipid-Based Nanoparticles for the Treatment of Alzheimer's Disease

NPs, such as SLNs and NLCs, offer an effective strategy for encapsulating RES, thereby enhancing the oral bioavailability of this poorly soluble lipophilic compound.<sup>174</sup> Neves et al developed RES-loaded SLNs and NLCs to improve the physicochemical properties of RES and enhance its oral bioavailability for potential neurological disorder treatments.<sup>174</sup> Their findings demonstrated that both formulations significantly reduced RES instability *in vivo* while facilitating its sustained release, positioning these nanomedicines as promising candidates for oral drug delivery. Vascular dementia (VaD), a leading cognitive disorder caused by cerebrovascular abnormalities, has shown increasing associations with mitochondrial dysfunction and oxidative stress. Recent studies have investigated the therapeutic efficacy of RES-loaded SLNs (R-SLNs) in a VaD animal model induced by permanent bilateral common carotid artery occlusion.<sup>175</sup> The formulation exhibited superior pharmacokinetic properties, achieving a 4.5-fold increase in cerebral RES bioavailability compared to the non-encapsulated form. Behavioral assessments revealed that R-SLN treatment resulted in significantly greater cognitive improvements in VaD rats than conventional RES treatment. Additionally, oral delivery of R-SLNs effectively suppressed mitochondrial-derived reactive oxygen species (ROS) production and inhibited lipid peroxidation cascades within the VaD model. These results suggest that R-SLNs are a promising therapeutic platform for both VaD management and neurodegenerative diseases, such as AD, by enhancing BBB penetration and providing targeted antioxidant delivery. Khishvand et al developed RES-loaded SLNs (RSV-SLNs) and optimized their physicochemical properties.<sup>176</sup> Behavioral assessments demonstrated that RSV-SLNs significantly reduced escape latency and improved target quadrant retention time, outperforming free RES. Histopathological analysis showed that RSV-SLNs exhibited neuroprotective effects, reducing neurodegeneration and preserving the morphological integrity of CA1 pyramidal cells. Additionally, the nanoformulation demonstrated superior therapeutic potential in modulating oxidative stress, significantly lowering brain lipid peroxidase levels and elevating GSH concentrations. These findings indicate that RSV-SLNs offer enhanced therapeutic benefits over conventional RES in alleviating AD-related pathological features. To further enhance the brain-targeting ability of RSV-SLNs, a novel formulation of apolipoprotein E (ApoE)-functionalized RSV-SLNs (SLN-DSPE-ApoE RSV and SLN-Palmitate-ApoE RSV) was developed. By exploiting the recognition of ApoE by low-density lipoprotein (LDL) receptors on the BBB, this formulation aimed to improve NP targeting and delivery efficiency.<sup>177</sup> *In vitro* permeability assays using hCMEC/D3-derived BBB models demonstrated a 1.8-fold increase in transendothelial penetration for the surface-functionalized NPs compared to their non-functionalized counterparts. Loureiro et al designed a RES-loaded SLN functionalized with OX26 antibodies to inhibit A $\beta$  aggregation.<sup>178</sup> The results indicated that this nanomedicine exhibited a stronger inhibitory effect compared to free RES. Furthermore, *in vitro* studies using a BBB model demonstrated that the nanomedicine's BBB penetration was four times greater than that of

free RES. These findings suggest potential therapeutic benefits for the prevention or treatment of AD. However, further in vivo experiments are necessary to confirm these results. As an advanced generation of lipid-based NCs, NLCs have been effectively utilized for RES encapsulation. Rajput et al developed an in situ gel formulation incorporating RES-loaded NLCs (RES-NLCs) for intranasal administration in scopolamine-induced AD rats.<sup>179</sup> Comparative analysis revealed that the RES-NLCs in situ gel exhibited superior therapeutic efficacy in enhancing cognitive functions compared to its orally administered RES suspension-based in situ gel. Notably, the RES-NLCs in situ gel enhanced nasal mucosal permeability five-fold. In an innovative approach to targeted drug delivery, researchers developed a biomimetic nanoplatfrom by encapsulating RES within erythrocyte membrane-coated NLCs.<sup>180</sup> This system, designated as RVG/TPP NPs@RBCm, features dual surface modifications with RVG29 and TPP to improve both BBB penetration and mitochondrial targeting. Comparative analysis demonstrated that RVG/TPP NPs@RBCm administration significantly reduced A $\beta$  accumulation and oxidative stress markers in both in vitro and in vivo AD models, outperforming control and other treatment groups. Following intravenous administration, the nanoplatfrom showed sustained drug release, improved biocompatibility, and extended systemic circulation. These findings suggest that this biomimetic delivery system could offer a promising therapeutic strategy for neurodegenerative disorders.

### Resveratrol Delivery via Protein-Based Nanoparticles for the Treatment of Alzheimer's Disease

Malaiya et al developed and evaluated CS-coated BSA NPs for enhancing the therapeutic efficacy of RES (CS-RES-BSANPs) in the targeted treatment of AD in elderly females.<sup>181</sup> Characterization results demonstrated that the CS-RES-BSANPs exhibited spherical morphology with smooth surfaces and maintained excellent stability for 90 days under ambient refrigeration. In vitro release studies showed sustained drug release from CS-RES-BSANPs over 48 hours (cumulative release: 60.74%), compared to near-complete release of free RES (94.28%). Additionally, in vitro studies confirmed the biosafety of CS-RES-BSANPs, showing no significant alteration in the histological integrity of nasal mucosa. Behavioral assessments in AD rat models indicated that intranasally administered CS-RES-BSANPs significantly improved cognitive deficits compared to native RES, highlighting their potential as effective nose-to-brain drug delivery carriers.

## Conclusions

Currently, there is still a lack of therapeutic drugs that can effectively prevent or reverse the progression of AD. Notably, NCs of TCM delivery via NDDS for AD treatment bring hope to patients. Although both NCs of TCM and NDDS have limitations and there are relatively few clinical studies, these issues may be effectively resolved through the solutions described earlier. In conclusion, NDDS opens up new prospects for the application of NCs of TCM in AD treatment. In the future, with the rapid development of nanotechnology and continuous breakthroughs in research, the NCs of TCM delivery via NDDS will fully exert their pharmacological effects, enabling the exploration of more efficient and innovative therapeutic strategies for AD treatment.

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## Disclosure

The authors report no conflicts of interest in this work.

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