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# Nanotechnology-based targeted delivery strategies for the treatment of Alzheimer's disease

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Alzheimer's disease (AD), as a common neurodegenerative disorder, seriously affects human health. However, the treatment of AD has always faced significant challenges and has attracted extensive attention in medical research. In recent years, nanoparticle-based therapeutic strategies have been identified as a promising direction in AD research due to their unique advantages and potential. These strategies leverage the distinctive physical and chemical properties of nanomaterials, enabling them to effectively traverse the blood–brain barrier and directly target pathological sites, thereby minimizing damage to normal tissues and enhancing therapeutic efficacy. This approach holds considerable promise for AD treatment. Current literature indicates that nanomedicines can deliver therapeutic agents, such as approved pharmaceuticals, natural compounds, antibodies, and metal nanoparticles, directly to lesion sites, thereby reducing collateral damage to healthy tissues and improving treatment outcomes. With continuous advancements in nanotechnology and ongoing scientific investigations, there is potential for developing safer and more effective treatment options for AD patients in the future. This review aims to summarize recent developments in nanoparticle-based strategies for AD therapy and elucidate their mechanisms of action, providing new insights for the future development and advancement of nanomedicines in this domain.

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## 1 Introduction

Alzheimer's disease is recognized as the most prevalent form of progressive, persistent neurodegenerative disorder, characterized by cognitive and memory impairments and serving as the leading cause of dementia, predominantly affecting the elderly population.<sup>1</sup> According to estimates by the World Health Organization (WHO), over 55 million individuals globally are affected by dementia, with AD being the most common form, potentially accounting for 60–70% of cases.<sup>1–3</sup> In the United States alone, approximately 6.9 million individuals aged 65 and older are living with the impact of AD.<sup>1</sup> As a disease that impairs memory and cognitive abilities, although AD progresses slowly, it eventually renders patients bedridden and reliant on caregiving, imposing substantial economic and psychological burdens on both individuals and their families.<sup>4</sup> AD also poses significant challenges to aging societies. With increasing global life expectancy, the number anticipated to be living with the impact of AD is projected to reach 87 million by 2050, and the WHO notes that costs related to dementia, estimated to be \$1.3

trillion per annum in 2019, are expected to double to \$2.8 trillion by 2030.<sup>5</sup>

Alzheimer's disease is an exceedingly complex chronic neurodegenerative disorder attributed to a confluence of multiple pathogenic factors.<sup>6</sup> Among the various implicated pathological pathways, synaptic dysfunction, such as synaptic loss and deficits in synaptic plasticity, is closely associated with cognitive decline.<sup>7</sup> Neurotransmitter deficiencies also contribute to a multitude of neurodegenerative symptoms observed in AD, including cholinergic and glutamatergic deficits related to cognitive decline, excitatory and inhibitory neurotransmission imbalances leading to synaptic plasticity deficits and seizure-like symptoms, and monoaminergic neurotransmission deficits contributing to neuropsychiatric symptoms.<sup>8</sup> Several approved therapeutics alleviating AD symptoms are based on these mechanisms, such as donepezil, which acts as an acetylcholinesterase inhibitor (AChEI) by preventing the breakdown of acetylcholine (ACh) by acetylcholinesterase (AChE), thereby enhancing ACh concentrations and promoting neuronal communication.<sup>9,10</sup> In general, the major pathogenic hypotheses for AD can be broadly categorized into several aspects: the amyloid-beta ( $A\beta$ ) cascade hypothesis,<sup>11</sup> the tau hyperphosphorylation hypothesis,<sup>12</sup> mitochondrial dysfunction,<sup>13</sup> the oxidative stress hypothesis,<sup>13</sup> and neuroinflammatory responses.<sup>14</sup> It is essential to note that these pathogenic mechanisms do not exist in isolation but instead interact, collectively driving AD

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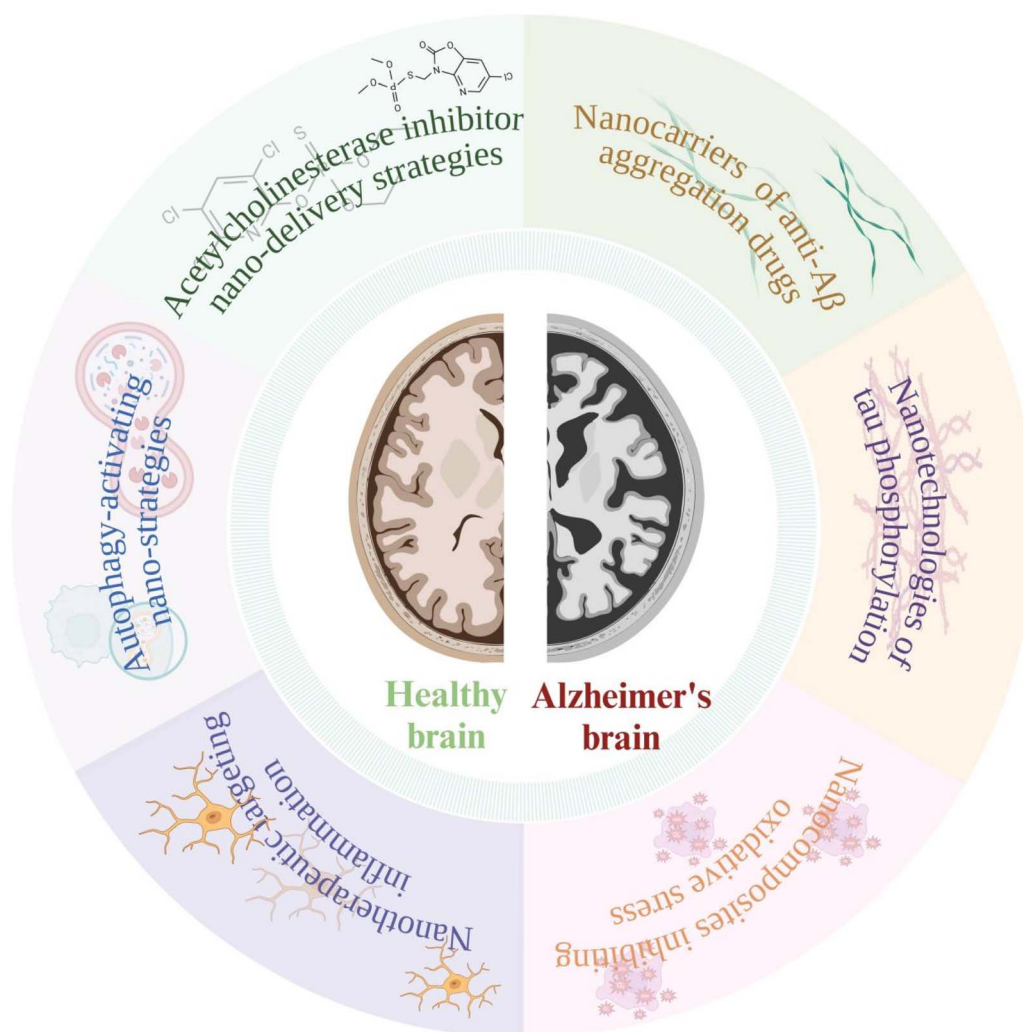


Fig. 1 Schematic diagram of various nano-targeted delivery strategies for Alzheimer's disease.

progression. Presently, scientists are exploring a range of therapeutic strategies, including drugs and treatments targeting amyloid proteins, tau proteins, inflammation, and neurotransmitters, to slow AD progression and improve patient quality of life.

Furthermore, therapeutic targets for AD primarily need to exert their effects within the brain. However, the presence of the blood–brain barrier (BBB) constitutes the greatest challenge to drug delivery into the brain (Fig. 2).<sup>15,16</sup> The BBB is a physical and biochemical barrier located between brain microvascular endothelial cells, comprising endothelial cells (ECs) connected *via* tight junctions, a basement membrane, pericytes, and astrocytic end-feet encircling the capillaries.<sup>17</sup> It is a complex interface that closely communicates with the rest of the central nervous system and is influenced by peripheral tissues. The primary function of the BBB is to selectively permit certain substances to enter the brain while blocking others, including pathogens and most drugs, from accessing brain tissue—a characteristic that also hinders most drugs from penetrating the brain.<sup>18</sup> It prevents most macromolecules and

approximately 98% of small molecules from entering the brain. This has propelled researchers to develop effective strategies or agents capable of penetrating the BBB to achieve targeted delivery of therapeutic agents.<sup>19</sup> Current approaches include the development of highly permeable and targeted nanomedicines or leveraging specific proteins or ligands to enhance drug translocation across the BBB.<sup>20</sup>

Given the aforementioned pathogenic mechanisms and the complexities of drug delivery, researchers have explored a variety of nanoparticle-based therapeutic strategies to intervene in AD.<sup>21–23</sup> We classify and summarize these strategies based on their primary therapeutic mechanisms as follows (Fig. 1): (1) acetylcholinesterase inhibitor nano-delivery strategies; (2) nanocarriers for the targeted delivery of anti-A $\beta$  aggregation drugs; (3) nanotechnologies for the targeted delivery of agents inhibiting abnormal tau phosphorylation; (4) nanotherapeutic approaches targeting inflammation to intervene in AD; (5) nanocarriers focused on BBB penetration; (6) nanocomposites inhibiting oxidative stress; (7) autophagy-activating nano-strategies. Detailed descriptions are provided below:



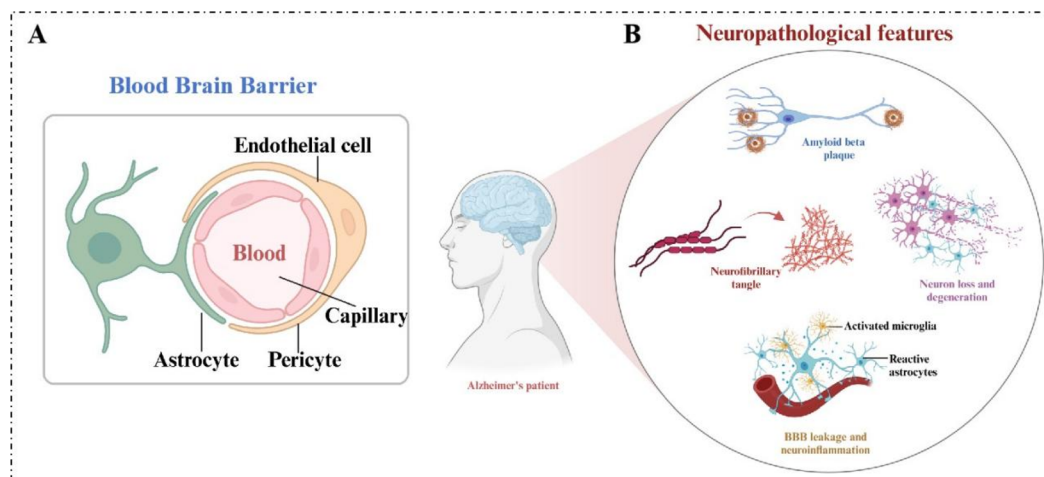


Fig. 2 (A) Detailed anatomical view of the blood–brain barrier, showing capillaries, endothelial cells, pericytes, the basal layer, and astrocytes. (B) Neuropathological features in the pathogenesis of AD.

### 1.1 Acetylcholinesterase inhibitor nanodelivery strategy

Acetylcholine is a neurotransmitter intrinsically linked to learning and memory, and augmenting acetylcholine levels can facilitate improved cognitive function in AD patients.<sup>24</sup> Inhibition of AChE is a common therapeutic strategy for AD. AChE

inhibitors prevent the breakdown of ACh, thereby increasing its concentration in the synaptic cleft and enhancing cholinergic neurotransmission. This augmentation of neuronal signaling can subsequently ameliorate cognitive functions.<sup>25</sup> Consequently, numerous nanoparticle strategies targeting AChE have been proposed (as depicted in Table 1).

Table 1 Summary table of acetylcholinesterase inhibitor nanodelivery strategies and molecular mechanisms

Name	Active drug	Carrier	Model ( <i>in vivo/in vitro</i> )	Therapeutic pathways	Ref.
—	Donepezil	Chitosan nanofibers	Male Wistar rats ( <i>in vivo</i> )	The absorption rate of donepezil was increased by chitosan nanofibers	28
Donepezil free base-nanostructured lipid carriers (DPB-NLC)	Donepezil	NLC gel	Franztype diffusion cells ( <i>in vitro</i> skin permeation study)	Improve the skin permeability of the drug and increase the flux of the drug through the skin	29
Carrier-free nanomodulator (NanoDS)	Donepezil	Simvastatin	FAD <sup>4T</sup> transgenic mice ( <i>in vivo</i> )	Brain delivery <i>via</i> the nasal route and overcoming the associated gastrointestinal (GIT) side effects	33
Nanostructured lipid carriers of donepezil hydrochloride (DNZ NLC)	Donepezil hydrogen	Nigella sativa (NS)	Male Sprague Dawley rats ( <i>in vivo</i> )	Improves nasal permeability and enhances drug distribution in the brain	32
Nano-lipid drug conjugates (LDC-NPs)	PAMs of M1 receptors	Nano-lipid	—	It improves bioavailability, improves efficacy, and reduces the therapeutic dose and side effects	34
Memantine-encapsulated polymeric nanoparticles	Memantine	—	Sprague Dawley rats ( <i>in vivo</i> )	It has no toxic effect on cells, and the absorption of the drug at the target site is higher	35
—	Piaglitazone	Nano-lipid carrier	Male Wistar rats ( <i>in vivo</i> )	The nasal permeability of PIO <i>in vitro</i> was improved	36
—	AChE inhibitor	GO	—	Can cross the blood–brain barrier, enhance free radical scavenging capabilities, and achieve additional therapeutic benefits through bionnanometer synergies	37
Tacrine-hydroxyphenylbenzimidazole (TAC-BIM)	Tacrine (TAC)	Benzimidazole (BIM)	SH-SY5Y cells ( <i>in vitro</i> )	Higher AChE inhibitory activity, high inhibition of A $\beta$ aggregation, and moderate free radical scavenging activity and metal chelating ability	38



Donepezil is a widely utilized acetylcholinesterase inhibitor that enhances acetylcholine levels by inhibiting AChE activity within the brain.<sup>26</sup> Since its approval in the late 1990s for the treatment of AD, donepezil has become a standard pharmacological intervention, primarily used for mild to moderate AD.<sup>27</sup> Multiple clinical trials have demonstrated that donepezil significantly improves or maintains cognitive function and quality of life in patients. Despite its overall favorable safety profile, adverse effects such as nausea, vomiting, diarrhea, and insomnia may occur. Hence, employing nanotechnology for targeted drug delivery to enhance efficacy while reducing side effects is a current research focus.

Nonetheless, oral administration of donepezil in clinical practice is fraught with drawbacks that often lead to poor patient adherence. Therefore, developing nanoparticulate formulations of donepezil capable of traversing the blood–brain barrier or nasal epithelium is crucial to address gastrointestinal side effects associated with oral delivery. Researchers have developed a spectrum of nanoparticle formulations using delivery-competent and biocompatible materials, including chitosan nanofibers, nanostructured lipid gels, hyaluronic acid, and self-assembled nano-drugs.<sup>28–31</sup> Notably, Tekade and colleagues engineered a nanostructured lipid carrier containing donepezil hydrochloride (DNZ HCl) for the effective management of AD. This nanoparticle formulation significantly enhanced nasal permeability and directly delivered the drug to the brain, bypassing the BBB.<sup>32</sup> Moreover, Duan *et al.* devised a carrier-free nano-modulator (NanoDS) *via* the self-assembly of donepezil and simvastatin, which facilitated rapid and efficient transmucosal passage across the nasal epithelium, achieving subsequent drug release and multiple therapeutic effects.<sup>33</sup> Furthermore, to mitigate donepezil-induced adverse reactions such as nausea, vomiting, and dizziness, Chintamaneni *et al.* proposed surface-engineered nanolipid drug conjugates with M1 receptor positive allosteric modulators (PAMs) to enhance brain bioavailability, thereby reducing therapeutic dosage and side effects.<sup>34</sup> Liu *et al.* also offered a nanoliposome carrier based on spice-derived antioxidants as a potential “green” alternative to synthesized AChE inhibitory drugs.<sup>22</sup> Additionally, targeted brain delivery strategies have also been designed for marketed AD drugs, memantine, and pioglitazone.<sup>35,36</sup>

Beyond nanoparticulate delivery for existing medications, numerous nanoparticle therapeutic strategies have been developed based on the pathogenetic mechanism of AChE inhibition. Phanrang *et al.* integrated AD drugs into graphene oxide (GO) nanocomposites, facilitating targeted drug delivery across the blood–brain barrier, thereby more effectively inhibiting AChE in AD patients.<sup>37</sup> Chitosan, with its commendable biocompatibility, bioadsorbability, and degradable products, has been utilized in conjunction with the natural cholinesterase inhibitor galantamine to create an innovative intranasal nano-drug delivery system for AD treatment, aimed at AChE inhibition.<sup>31</sup> Additionally, novel tacrine-hydroxyphenyl-benzimidazole (TAC-BIM) hybrids exhibited greater AChE inhibitory activity (IC<sub>50</sub> in the nanomolar range) and significantly repressed both self- and Cu-induced A $\beta$  aggregation (up to 75%) compared to the monotherapy of tacrine (TAC).<sup>38</sup>

However, AChE inhibitors primarily provide symptomatic relief and do not halt or decelerate the progression of AD. As the disease advances, drug efficacy may wane. Thus, integration with other therapeutic modalities remains necessary to comprehensively address this complex disease.

## 1.2 Targeted nanocarriers for the delivery of anti-A $\beta$ aggregation drugs

Amyloid-beta (A $\beta$ ) is a pivotal protein in the pathogenic progression of AD. It is derived from the amyloid precursor protein (APP) *via* enzymatic cleavage and can form toxic aggregates. These aggregates accumulate in the brains of AD patients as insoluble fibers and plaque deposits, known as amyloid plaques. These plaques are pervasive in the brains of AD patients, particularly in the hippocampal and cortical regions, which are closely associated with memory and cognitive functions. A $\beta$  aggregates disrupt intracellular signaling, leading to neuronal dysfunction and cell death. They may also trigger inflammatory responses, further damaging brain tissue. Despite the crucial role of A $\beta$  in the pathology of AD, therapeutic strategies targeting A $\beta$  have not yet achieved groundbreaking success. Currently, no pharmacological agents effectively clear or prevent the formation of A $\beta$  deposits in the brain. Therefore, identifying therapeutic approaches that inhibit A $\beta$  aggregation or promote its disaggregation is a primary research objective in AD studies. Various nanoparticle-based therapeutic strategies targeting A $\beta$  aggregation have been developed (as shown in Table 2), which can be broadly categorized into nano-carriers loaded with botanical extracts, combination-type nanomaterials, functional nanomaterials, and biomembrane-based nanomaterials, as elaborated below:

Certain herbal extracts (*e.g.*, silymarin (SIL),<sup>39,40</sup> quercetin (Que),<sup>41–43</sup> cannabidiol (CBD),<sup>44</sup> ApoE-PLGA,<sup>45</sup> rutin (Cur),<sup>46</sup> nattokinase,<sup>47</sup> and curcumin,<sup>48,49</sup> among others<sup>50</sup>) possess characteristics for disrupting amyloid aggregates, exhibiting antifibrinolytic activity, and mitigating A $\beta$ -induced cytotoxicity, thereby holding potential for clinical AD treatment. However, these extracts are constrained by poor solubility and inability to reach target sites. Consequently, researchers have developed a variety of nano-carriers (*e.g.*, carbon dots, poly(lactic-co-glycolic acid) (PLGA), water-soluble PLGA, *etc.*) to overcome these limitations and facilitate the targeted delivery of herbal extracts.

The application of combination-type nanomaterials also offers a novel direction for the development of therapeutic modalities. By physical and chemical amalgamation of two or more nanomaterials or therapeutic agents, these combinations enhance delivery efficacy or targeting capacity while preserving drug activity, thus achieving enhanced therapeutic efficacy with reduced adverse effects. Several combinatory strategies have emerged in recent years.<sup>51–56</sup> A typical example is the work of Singh *et al.*, who conjugated multifunctional poly(amidoamine) (PAMAM) dendrimers with tocopheryl polyethylene glycol succinate-1000 (TPGS), creating a PIP-TPGS-PAMAM dendrimer complex to mitigate the toxicity of A $\beta$ 1–42 fibrils on SHSY5Y cells.<sup>57</sup> Similarly, Huang *et al.* utilized monosialotetrahexosylganglioside (GM1)-modified reconstituted



Table 2 Summary table of nanocarriers targeting the delivery of anti-A $\beta$  aggregation drugs and molecular mechanisms

Name	Active drug	Carrier	Model ( <i>in vivo/in vitro</i> )	Therapeutic pathways	Ref.
Silibinin encapsulated nanoliquid crystalline (SIL-NLCS)	Silibinin (SIL)	Silibinin (NLCS)	Balb/c mice ( <i>in vivo</i> )	SIL-NLCS showed a higher protective effect against A $\beta$ 1–42 toxicity	39
Nano-liquid crystals silibinin (SIL-NLCS)	Silibinin (SIL)	Nano-liquid crystals (NLCS)	Wistar rats ( <i>in vivo</i> )	SIL is encapsulated in nanoscale liquid crystals (NLCS) to increase the payload in the brain	40
Red emission carbon dots (R-CD-75)	Que	CDs	SH-SY5Y cell ( <i>in vitro</i> )	R-CD-75 significantly inhibited A $\beta$ aggregation and rapidly depolymerized mature A $\beta$ fibers, and significantly reduced A $\beta$ -induced cytotoxicity	41
Triphenylphosphonium-modified quercetin-derived smart nanomedicine (TQCN)	TQCN	Nano-chitosan	AD mice ( <i>in vivo</i> )	TQCN coated with nano-chitosan can reduce A $\beta$ plaques and increase brain CB1 and CB2 levels	42
Apolipoprotein E4-lactide-co-glycolide (ApoEPLGA)	ApoE	PLGA	—	The prepared metal chelating agent nanoformula exhibits blood–brain barrier penetration	45
Selenium-poly-lactide-co-glycolide (Se-PLGA)	Se NPs	PLGA	AD mice ( <i>in vivo</i> )	Se-PLGA can bind specifically to A $\beta$ plaques	46
LGA-encapsulated nattokinase polymeric nanoparticles	Nattokinase	PLGA	Phosphate buffer ( <i>in vitro</i> )	PLGA-encapsulated nattokinase polymerized nanoparticles can down-regulate amyloid aggregation and exhibit anti-fibrinolytic activity	47
PLGA coated-curcumin NPs	Curcumin	PLGA	GI-1 cells ( <i>in vitro</i> )	It destroys amyloid aggregates, exhibits antioxidant properties, and is non-cytotoxic	48
Nanoliposomes decorated with a curcumin derivative	Curcumin	Nanoliposomes	—	These nanoparticles have a very high affinity for A $\beta$ 1–42 fibril	49
Amphipathic dipeptide vesicle-templated selenium nanoparticles (RAF-SeNPs)	RAF	SeNPs	AD mice ( <i>in vivo</i> )	RAF-SeNPs showed neuroprotective effects and reduced A $\beta$ 42 aggregation load in tissues	51
—	Antibody 6H4 fragments	Polymer nanomicelles	AD mice ( <i>in vivo</i> )	By providing enough antibodies in the brain to reduce the A $\beta$ protein	52
—	Anti-amyloid-beta (anti-A $\beta$ ) scFv	Pluronic	Artificial cerebrospinal fluid ( <i>in vitro</i> )	Pluronic micelles in nanocoliters help to increase the stability of anti-A $\beta$ scFv in plasma	53
PCN-222 metal–organic framework and indocyanine green (PCN-222@ICG@RVG)	PCN-222	ICG@RVG	Brain-on-a-chip model ( <i>in vitro</i> )	PCN-222@ICG@RVG can effectively decompose A $\beta$ plaques and reduce neurotoxicity	54
Apolipoprotein E3-reconstituted high density lipoprotein (ApoE3-rHDL)	—	—	SAMP8 mice ( <i>in vivo</i> )	ApoE3-rHDL reduced A $\beta$ deposition, alleviated microglia, and improved neurological changes	56
Piperine-tocopheryl polyethylene glycol succinate-1000-multi-functional polyamidoamine (PIP-TPGS-PAMAM)	Piperine (PIP)	TPGS-PAMAM	SHSY5Y cells ( <i>in vitro</i> )	Alleviates the toxicity of A $\beta$ 1–42 fibrils on SHSY5Y cells	57
$\alpha$ NAP-monosialotetrahexosylganglioside (GM1)-modified reconstituted high density lipoprotein (GM1-rHDL)	GM1-rHDL	$\alpha$ NAP	AD mice ( <i>in vivo</i> )	It effectively reduces A $\beta$ deposition, improves neurological changes, and rescues memory loss without cytotoxicity	58





Table 2 (Contd.)

Name	Active drug	Carrier	Model ( <i>in vivo/in vitro</i> )	Therapeutic pathways	Ref.
8-HQ-based polymer (DHQ)	8-Hydroxyquinoline (8-HQ)	—	HeLa-RFP-Rab5 cells ( <i>in vitro</i> )	DHQ delivers superoxide dismutase to target cells, thereby reducing intracellular ROS levels	59
CRISPR/Cas9 plasmids (CF-TBIO)	CRISPR/Cas9	F-TBIO	2 × Tg-AD mice ( <i>in vivo</i> )	CF-TBIO can knock out the BACE1 gene and reduce the burden of amyloid beta	60
Ca-polyP microparticles (ca-polyP-MP)	—	—	Rat primary cortical neurons ( <i>in vitro</i> )	The decrease in beta-amyloid-induced adenosine triphosphate (ATP) levels was reversed by Ca-polyP-MP	61
Chondroitin sulphate (CS)-modified MoS <sub>2</sub> nanoenzyme (CS@MoS <sub>2</sub> )	MoS <sub>2</sub>	CS	D-Gal/AICl <sub>3</sub> -induced AD mice ( <i>in vitro</i> )	CS@MoS <sub>2</sub> inhibited the aggregation of Aβ1–40 and prevented the toxic damage caused by Aβ1–40	63
C <sub>3</sub> N nanodots	—	—	AD mice ( <i>in vivo</i> )	The C <sub>3</sub> N nanodots mitigated neuronal toxicity caused by aggregation and prevented neurite damage	64
Niobium carbide nanozyme	—	—	Male ICR mice ( <i>in vivo</i> )	Inhibition of Cu <sup>2+</sup> induced accumulation of Aβ peptide and clearance of excess cell ROS	65
Aβ-targeting peptide (LPFFD) modified HF-metal–organic frameworks (MOFs)	HF-MOFs	LPFFD	AD mice ( <i>in vivo</i> )	LPFFD-modified hf-mof can reduce Aβ-induced neurotoxicity	66
Gd@C(82)	—	—	AD mice ( <i>in vivo</i> )	The β-peptide-induced neuronal cytotoxicity was significantly alleviated	67
HSA-manganese dioxide nanocomposites (HMn NCs)	HSA	MnO <sub>2</sub> NCs	CL2006 worms ( <i>in vivo</i> )	HMn NCs exhibit excellent reactive oxygen scavenging ability. Moreover, it can alleviate Aβ-mediated SH-SY5Y neurotoxicity	68
g-C <sub>3</sub> N <sub>4</sub> /CoP	g-C <sub>3</sub> N <sub>4</sub>	CoP	AD mice ( <i>in vivo</i> )	The photothermal properties of g-C <sub>3</sub> N <sub>4</sub> and CoP can inhibit Aβ and reduce the deposition of Aβ in the brain	69
Tryptophan nanoparticles (TNPs)	—	—	Streptozotocin-administration-induced AD phenotype in rats ( <i>in vivo</i> )	TNPs can significantly inhibit amyloid model dipeptide, phenylalanine–phenylalanine (FF) formation of fibers	70
(E)-1-(2-(2-Methoxyethoxy)ethyl)-4-(2-(9-methyl-9H-carbazol-3-yl)vinyl) quinolinium iodide (me-slg)	me-slg	—	—	me-slg binds specifically to Aβ1–40 fibrils through electrostatic and van der Waals interactions	71
Iminodiacetic acid-conjugated nanoparticles (IDA-NPs)	—	—	SH-SY5Y cells ( <i>in vitro</i> )	Inhibition of Aβ42 aggregation and reduction of Zn <sup>2+</sup> accelerated cytotoxicity	72
ALZc3	—	—	Male rats ( <i>in vivo</i> )	ALZc3 can significantly prevent memory impairment and Aβ (1–42) toxicity	73

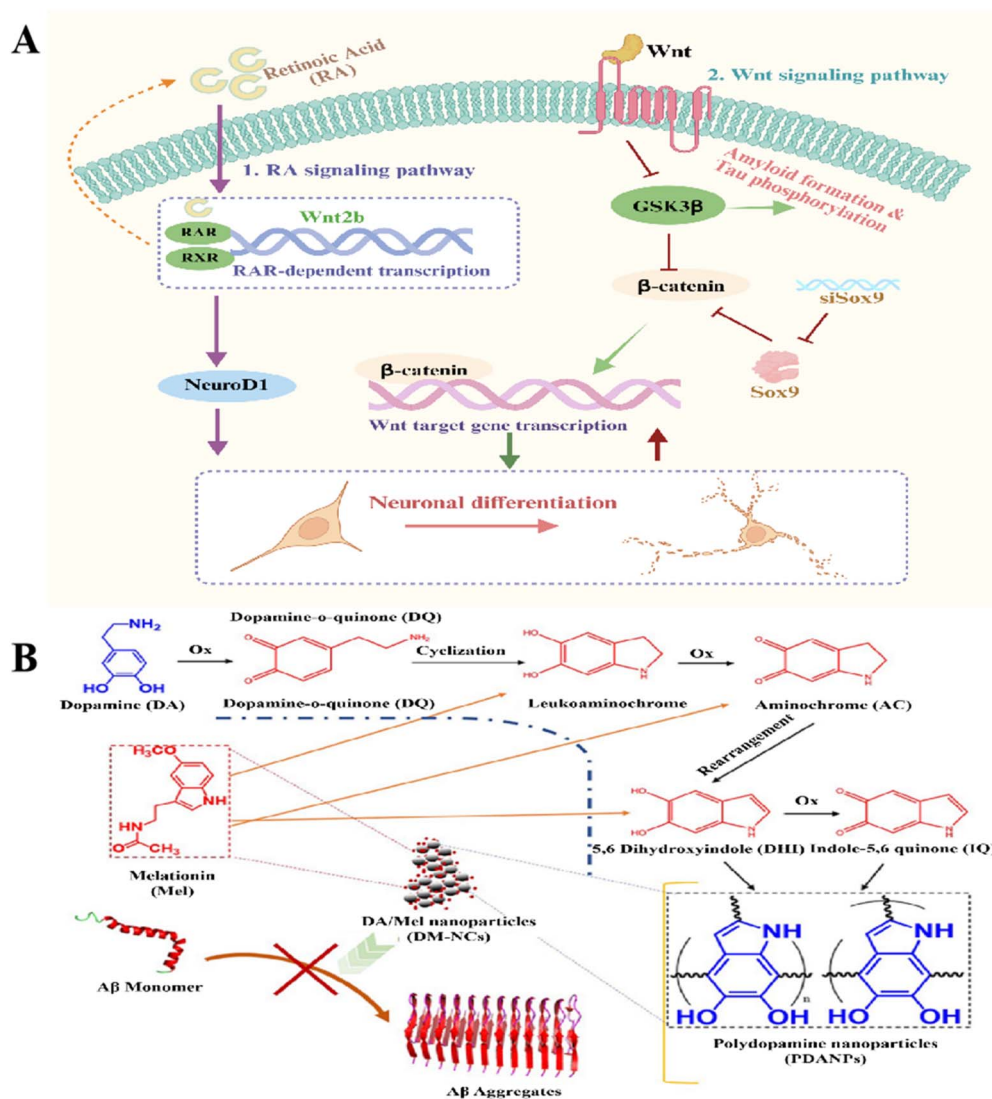


Fig. 3 (A) Schematic of signaling pathways for NSC differentiation regulated by the PPAR-siSOX9 nanoformulation;<sup>77,81</sup> (B) schematic illustrating the mechanism of DM-NC evolution and its A $\beta$  antiaggregation/disaggregation activity.<sup>78,82</sup>

high-density lipoprotein (GM1-rHDL) to construct a multifunctional nanostructure  $\alpha$ NAP-GM1-rHDL for better neuronal protection against A $\beta$ (1–42) oligomer-induced cytotoxicity.<sup>58</sup> These studies underscore that nanotechnology provides diversified strategies for AD treatment, offering new perspectives and tools from antioxidant enzyme delivery to gene editing, and from monotherapy to multifunctional therapeutics.<sup>59,60</sup>

Functional nanomaterials differ from combination-type nanomaterials as they primarily leverage the intrinsic properties of the nanomaterials themselves to inhibit A $\beta$  aggregation for AD treatment. Such nanomaterials primarily include metallic nanoparticles, nanozymes, carbon dots, nanochelators, and metal-organic frameworks, among others (Fig. 3).<sup>61–81</sup> For instance, Müller and colleagues synthesized an inorganic high-energy polymer polyphosphate (polyP) and discovered its capacity to reverse ATP level decline induced by amyloid-beta.<sup>61</sup> Karimi-Sales *et al.* synthesized ALZc3 *via* nano-complexation technology and evaluated its therapeutic effects

in a rat AD model, demonstrating that ALZc3 could notably prevent A $\beta$ (1–42) toxicity.<sup>73</sup> However, current studies lack direct comparisons between functional nanomaterials and conventional pharmaceuticals, and the biotoxicity and *in vivo* metabolism of these functional nanomaterials require further elucidation.

In future research, early-stage investigation of A $\beta$  aggregate formation and identification of novel therapeutic targets will remain focal points. By deepening the understanding of A $\beta$  pathogenic mechanisms, scientists aim to develop more effective therapies against this intricate neurodegenerative disease.

### 1.3 Targeted nanotechnology for the delivery of inhibitors against abnormal phosphorylation of tau protein

Tau protein is an intracellular protein within neurons that plays a crucial role in stabilizing the cytoskeleton and facilitating nutrient transport under normal conditions.<sup>81</sup> However, in AD, tau protein becomes hyperphosphorylated, leading to the



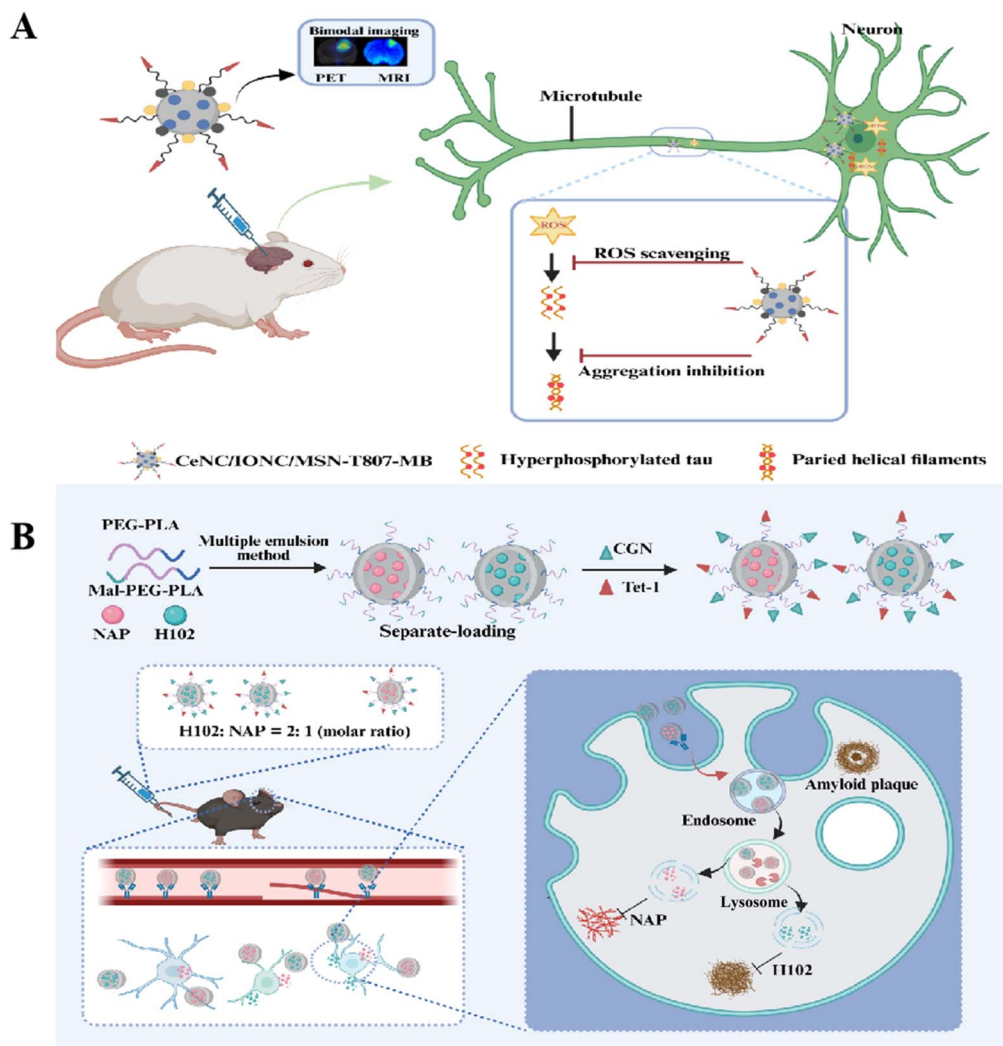


Fig. 4 (A) Schematic illustration of the designed synthetic procedure of a methylene blue (MB, a tau aggregation inhibitor) loaded nanocomposite (CeNC/IONC/MSN-T807) and its tau-targeted synergistic treatment.<sup>85</sup> (B) The optimized targeted nano\_x0002\_combination system, CT-NP/H102 + CT-NP/NAP (2 : 1), for synergistic peptide combination therapy at A $\beta$  and p-tau in AD. PEG-PLA nanoparticles (CT-NP)/H102 + CT-NP/NAP can effectively penetrate through the BBB and then accumu\_x0002\_late in diseased neurons by cascade targeting of CGN and Tet1 dual-modification. After endocytosis, the encapsulated peptides, H102 and NAP, were released intracellularly and interfered with A $\beta$  and tau pa\_x0002\_thology respectively to exert synergistic effects, thereby rescuing neurodegeneration and ameliorating cognitive impairment.<sup>86</sup>

formation of neurofibrillary tangles (NFTs). These tangles impair neuronal function and contribute to cognitive decline.<sup>82</sup> Thus, inhibiting tau hyperphosphorylation has emerged as a promising therapeutic approach for AD.<sup>83</sup> Nevertheless, targeting tau protein effectively remains challenging due to the impediment posed by the BBB. In this context, Liu *et al.*<sup>84</sup> and Chen *et al.*<sup>85</sup> (Fig. 4A), independently developed nanoparticle platforms utilizing nanomaterials as carriers to deliver methylene blue, both achieving targeted brain delivery to inhibit tau aggregation. Guo *et al.* also designed a nanocomposite system using polyethylene glycol-poly(lactic acid) copolymer (PEG-PLA) nanoparticles (CT-NPs) to inhibit tau hyperphosphorylation (Fig. 4B).<sup>86</sup> Additionally, Zhou *et al.* employed flower-shaped hollow ruthenium nanoparticles (Ru NPs) to devise a nerve growth factor (NGF) delivery system capable of suppressing tau hyperphosphorylation and significantly improving learning and

memory in AD mouse models.<sup>87</sup> Currently, several tau-targeting antibody therapeutics have exhibited potential in early clinical trials, although further validation of their efficacy and safety in long-term treatment is warranted.

#### 1.4 Targeted inflammation intervention for AD nanotherapeutic approaches

Recently, neuroinflammation has been underscored as a critical aspect of the pathogenesis of AD. Neuroinflammation refers to the inflammatory responses within the central nervous system, primarily mediated by microglia and astrocytes.<sup>88</sup> In the brains of AD patients, aberrant activation of microglia can induce neuroinflammation, thereby exacerbating neurodegenerative processes.<sup>89</sup> Given that neuroinflammation is a pivotal factor in AD progression, the targeted delivery of anti-inflammatory nano-therapeutics may offer valuable insights for developing





Table 3 Summary table of nanocarriers that penetrate the blood–brain barrier and molecular mechanisms

Name	Active drug	Carrier	Model ( <i>in vivo/in vitro</i> )	Therapeutic pathways	Ref.
Intelligent oral brain-targeting nanoparticle (FTY@Man NP)	FTY	PLGA-PEG	AD mice ( <i>in vivo</i> )	FTY@Man oral administration of NPs can efficiently cross multiple barriers	99
Citicoline sodium (CIT)-HA*TBLS	Citicoline sodium	HA*TBLS	AD induction was performed by using aluminum chloride (AlCl <sub>3</sub> ) ( <i>in vivo</i> )	By decorating hyaluronic acid to enable enhanced drug delivery from the nose to the brain	100
Hexagonal boron nitride (hBN)-folic acid (FA)	FA	hBN	SHSY5-Y cell ( <i>in vitro</i> )	The hBN-FA drug carrier system was assembled with a new drug candidate and a new boron-based hybrid to form a nanotransport system	101
—	3D6 antibody fragments (3D6-Fab)	Polymetric nanomicelle	AD mice ( <i>in vivo</i> )	The polymer nanomicelle (PM) system is capable of delivering 3D6-fab to the brain parenchyma to inhibit A $\beta$ aggregation	102
Quercetin-modified sulfur nanoparticles (Qc@SNPs) in microbubbles (MB)	Qc@SNPs	MB	AD mice ( <i>in vivo</i> )	Microvesicles combined with focused ultrasound were used to mediate the instantaneous opening of the blood–brain barrier and the delivery of nanomedicine	103
Casein coated-gold nanoparticles ( $\beta$ Cas AuNPs)	AuNPs	$\beta$ Cas	Zebrafish model ( <i>in vivo</i> )	$\beta$ Cas AuNPs are transported across the blood–brain barrier and sequestered A $\beta$ 42 and its induced toxicity in the brain in a non-specific, chaperon-like manner	104
Mesoporous nano-selenium (MSe) release delivery system (MSe-Res/Fc- $\beta$ -CD/Bor)	Res	Res/Fc- $\beta$ -CD	APP/PS1 mice ( <i>in vivo</i> )	MSe-Res/Fc- $\beta$ -CD/Bor first releases Bor by interacting with blood or cellular lactase, allowing the nanosystem to cross the blood–brain barrier (BBB)	105
$\beta$ -Sheet breaker peptide H102 (TQNP/H102)	H102	TGN/QSH	AD mice ( <i>in vivo</i> )	Two targeting peptides TGN and QSH were coupled to the surface of nanoparticles for blood–brain barrier transport and targeting A $\beta$ 42, respectively	106
Res and Sal encapsulated in liposomes-modified with ApoE (ApoE-Res/Sal-Lips)	Res/Sal	ApoE lips	APP/PS1 mice ( <i>in vivo</i> )	ApoE-Res/Sal-Lips enhance BBB permeability and improve transport efficiency	107
Angiopep-2 was modified on the surface of liposomes (Ang-Sal/Ica-Lip)	Sal/Ica	Angiopep-2	APP/PS1 mice ( <i>in vivo</i> )	The targeted molecule angiopep-2 is modified on the surface of liposomes, so that the constructed nanomedical drug delivery system can effectively cross the BBB and play an anti-AD role	108
TGN decorated erythrocyte membrane-coated poly (lactic-co-glycolic acid) nanoparticle (TRNNs)	—	—	AD mice ( <i>in vivo</i> )	Functional bionic nanoparticles can increase naringenin accumulation in the brain, allowing the drug to exert a greater therapeutic effect	109
Molybdenum disulfide quantum dots (MoS <sub>2</sub> QDs)-macrophage membrane (MM)	MoS <sub>2</sub> QDs	MM	APP/PS1 mice ( <i>in vivo</i> )	MoS <sub>2</sub> QDs have a targeted therapeutic effect on ROS elimination and anti-A $\beta$ 1–42 deposition, while the modification of MM can effectively target the brain	110
Erythrocyte membrane-camouflaged nanodrug delivery system (TR-ZRA)	CD22shRNA	Zn-CA	AD mice ( <i>in vivo</i> )	TR-ZRA can cross the blood–brain barrier, enhancing the ability of microglia to engulf A $\beta$ and reducing inflammation levels	111
Traceable CNS delivery nanoformulation (RVG-NV-NPs)	Bex/AgAuSe QDs	NSC membranes	AD mice ( <i>in vivo</i> )	RVG-NV-NPs are able to penetrate the blood–brain barrier and target nerve cells, extending blood circulation	112



Table 3 (Contd.)

Name	Active drug	Carrier	Model ( <i>in vivo/in vitro</i> )	Therapeutic pathways	Ref.
Pentaethylenhexamine (PEHA)-derived carbon dots (CDs)	—	—	Zebrafish model ( <i>in vivo</i> )	PCDs have very low cytotoxicity and can cross the blood–brain barrier (BBB)	113
Nano C60	—	—	APP/PS1 mice ( <i>in vivo</i> )	Granular C60 was able to cross the blood–brain barrier and promote the transport of phosphorylated CamKiz from the cytoplasm to synapses in A $\beta$ 42 oligomer-treated cells and APP/PS1 mice	114
Novel indocyanine green-modified graphene quantum dot nano-assemblies (NBGQDs-ICGs)	—	—	Microglia ( <i>in vitro</i> )	NBGQDs-ICGs can penetrate the blood–brain barrier, effectively weaken the adhesion of A $\beta$ 42 aggregates to the cell surface, and promote the phagocytosis of A $\beta$ 42 by microglia	115
CT/siRNA	BACE1 siRNA	PEG-PDMAEMA	APP/PS1 mice ( <i>in vivo</i> )	CT/siRNA nanocomplexes are able to specifically target BACE1 siRNA to brain neurons	117

novel treatments. Nonetheless, certain anti-inflammatory agents exhibit poor solubility in aqueous environments or compromised stability during formulation. In this regard, Tiozzo *et al.* refined the nasal-brain delivery of flurbiprofen for early AD-related neuroinflammation by formulating flurbiprofen acid and flurbiprofen sodium salt, demonstrating advantages in rapid dissolution and swift *in vitro* transport across rabbit nasal mucosa.<sup>90</sup> Subsequently, nanoparticles encapsulating the anti-inflammatory agent bryostatatin-1 and gold nanocages loaded with fingolimod hydrochloride have been developed to enhance therapeutic efficacy and fortify targeted delivery capabilities.<sup>91,92</sup> Exosome formulations engineered through genetic techniques have also been shown to significantly downregulate pro-inflammatory genes IL1 $\alpha$ , TNF $\alpha$ , and NF- $\kappa$ B while upregulating the anti-inflammatory gene IL10.<sup>93</sup> In addition, a recent modular nano-platform proposed by Liu *et al.*, composed of peptide-drug conjugates and an inflammation-responsive core, has been reported to facilitate transcellular transport across the blood–brain barrier, reduce levels of toxic proteins and inflammation, and ameliorate learning and memory deficits.<sup>22</sup> However, these approaches face certain limitations and challenges. For instance, prolonged use of anti-inflammatory medications may lead to adverse effects. Moreover, neuroinflammation is a complex biological process involving multiple cell types and signaling pathways.<sup>94</sup> A singular pharmacological agent may not comprehensively suppress inflammatory responses, underscoring the need for the development of combinatory therapeutic strategies targeting multiple pathways.

### 1.5 Nanocarriers that penetrate the blood–brain barrier

The BBB is an anatomical protective barrier that separates the brain from direct contact with systemic circulation.<sup>95</sup> It constitutes a vital component of the neurovascular unit, facilitating communication with the central nervous system while restricting the free exchange of substances within brain cells. The primary constituents of the BBB include endothelial cells, astrocytic end-feet, the basement membrane, tight junctions, and pericytes.<sup>96–98</sup> Despite the availability of numerous pharmaceuticals for neurological disorders, the specialized microvascular structure of the BBB permits the selective passage of only a limited number of drugs following systemic administration, resulting in suboptimal therapeutic efficacy.

In recent years, various nanoformulations based on nanocarriers, broadly classified into nanoparticles, liposomes, cell membranes, carbon dots, polymers, and others, have been developed to penetrate the BBB for the treatment of AD (as illustrated in Table 3). These nanostrategies offer controlled drug delivery, prolonged circulation time, targeted specificity, and enhanced efficacy, most importantly reducing toxicity through a biomimetic approach. Below is a comprehensive description of different types of nanocarriers and delivery systems:

Researchers have developed a series of nanoparticle-based intelligent delivery systems for the treatment of AD. Notably, oral brain-targeting nanoparticles (FTY@Man NP) employ

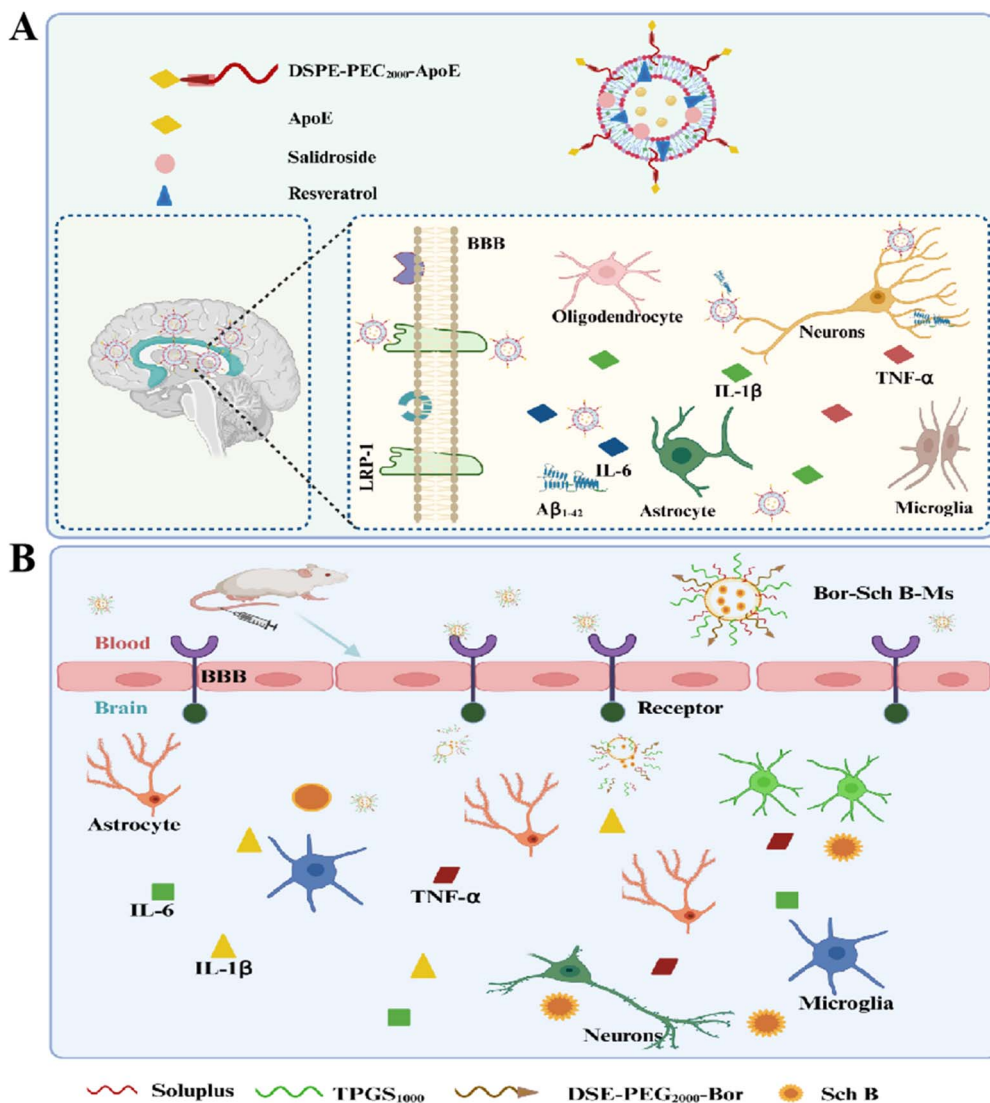


Fig. 5 (A) Targeting mechanism *in vivo* of ApoE-Res/Sal-Lips.<sup>117</sup> (B) Schematic illustration of the strategy for improving AD-related pathology by using borneol-modified *Schisandra B* micelles (Bor-Sch B-MB).<sup>31</sup>

a glucose-modulating strategy to effectively traverse multiple barriers, enabling multi-targeted therapy.<sup>99</sup> The citicoline sodium (CIT) drug is encapsulated within sphingosine and modified with hyaluronic acid, resulting in enhanced nasal-to-brain drug delivery.<sup>100</sup> The hexagonal boron nitride (hBN)-folic acid (FA) system integrates folic acid motifs into hexagonal boron nitride nanoparticles for AD therapy.<sup>101</sup> Polymeric nanomicelle PM systems deliver 3D6 antibody fragments to inhibit Aβ aggregation.<sup>102</sup> The quercetin-modified sulfur nanoparticles (Qc@SNPs) in microbubbles (MB) nanosystem utilizes focused ultrasound technology to temporarily open the BBB for nanoparticle delivery.<sup>103</sup> Casein coated-gold nanoparticles (βCas AuNPs) successfully abrogate Aβ toxicity in a zebrafish model.<sup>104</sup> The mesoporous nano-selenium (MSe) release delivery system (MSe-Res/Fc-β-CD/Bor) employs resveratrol-loaded β-cyclodextrin nanovalves, facilitating passage through the BBB by releasing Bor.<sup>105</sup> Additionally, a bifunctional nanoparticle drug delivery system loaded with the β-sheet breaker peptide H102

(TQNP/H102) is designed specifically for BBB transport and Aβ<sub>42</sub> targeting.<sup>106</sup> These innovative systems provide novel strategies for AD treatment, with the potential to enhance therapeutic outcomes.

Liposomal drug delivery systems have also been engineered to improve BBB penetration. The Res and Sal encapsulated in the liposome modified with ApoE (ApoE-Res/Sal-Lips) system significantly enhances BBB permeability and drug transport efficiency by modifying the liposome surface with ApoE.<sup>107</sup> Similarly, the Ang-Sal/Ica-Lip system encapsulates the neuroprotective agents salidroside (Sal) and icariin (Ica) within liposomes, employing angiopep-2 as a targeting ligand to efficiently cross the BBB and enhance therapeutic efficacy.<sup>108</sup>

The use of cell membranes as drug delivery vectors leverages the intrinsic properties of biological membranes by encapsulating drug molecules within the cell membrane, forming nanoparticles or micelles physically or chemically. For example, TGN decorated erythrocyte membrane-coated poly (lactic-co-





Table 4 Summary table of nanocomplexes that inhibit oxidative stress and molecular mechanisms

Name	Active drug	Carrier	Therapeutic pathways	Ref.
Ce NPs and geniposide and harpagoside (GH/CeO <sub>2</sub> NPs)	—	AD mice ( <i>in vivo</i> )	GH/CeO <sub>2</sub> NPs have redox and antioxidant properties, inhibit fibril formation and protein aggregation, and have the ability to combat tau protein aggregation and amyloid beta 1–42 aggregation	122
Flower-like Res-loaded selenium nanoparticles/chitosan nanoparticles (Res@SeNPs@Res-CS-NPs)	Res	AD mice ( <i>in vivo</i> )	Res@SeNPs@Res-CS-NPs can restore intestinal microbiota homeostasis to reduce neuroinflammation and inhibit Aβ aggregation and tau phosphorylation <i>via</i> the JNK/AKT/GSK3β signaling pathway	123
Antioxidant therapeutic nanoplatform	Selected polyphenol-rich vegetal extracts Silibinin	Nano-sized functionalized liposomes HSA	The platform had a high blood–brain barrier crossing ability, salvaging ROS levels and preventing the aggregation of alpha-synuclein fibrils	125
Silibinin–human serum albumin (HSA) nanoparticles	—	SHSY5-Y cell ( <i>in vitro</i> )	The neuroprotective and antioxidant activities of silybin-HAS nanoparticles were higher than those of free silybin-HAS nanoparticles	126
Ellagic acid (EA)-loaded nanoparticles (EA-NPs)	Ellagic acid	—	The antioxidant biomarkers were significantly increased and TBA was significantly decreased in the EA-NP group	127
Nano-formulation of graphene oxide (GO) loaded with dauricine (Dau)	Dauricine	Graphene oxide	Graphene oxide loaded with Dau significantly reduced oxidative stress by increasing superoxide dismutase levels and decreasing reactive oxygen species and malondialdehyde levels <i>in vitro</i>	128
Biodegradable polyamhydride nanoparticles	Apocynin	Polyamhydride nanoparticles	The nano-formula has a good protective effect against oxidative stress-induced mitochondrial dysfunction and neuronal damage	130
Rosiglitazone nanoformulation	—	AD mice ( <i>in vivo</i> )	Thiazolidinedione nanoparticles play a neuroprotective role by increasing the mRNA expression of growth factors and inhibiting oxidative stress and neuroinflammation	131
Triphenylphosphonium-conjugated ceria nanoparticles	—	5 × FAD transgenic Alzheimer's disease mouse model ( <i>in vivo</i> )	Triphenylphosphine coupled cerium dioxide nanoparticles inhibit neuronal death in a mouse model	132
Resveratrol (RSV)-selenium (Se) nanoparticles (RSV-SeNPs)	Resveratrol	SeNPs	RSV-SeNPs up-regulated the expression of SIRT1 and decreased the expression of microRNA-134. It has antioxidant and anti-inflammatory effects and can improve neurocognitive function	133
Catechin-loaded chitosan–alginate nanocarriers	Catechin	Chitosan–alginate nanocarriers	Catechin-supported chitosan–alginate NPs significantly improved acetylcholinesterase activity, oxidative biomarkers, spatial memory and learning ability	134
Curcumin (Cur) through phenylboronic ester bond (VLC@Cur-NPs)	VLC	Cur-NPs	VLC@Cur-NPs significantly increased pericellular regeneration in mice, which improved neurovascular function and ultimately alleviated memory deficits	136
Chondroitin sulphate nano-selenium (CS@Se)	—	AD mice ( <i>in vivo</i> )	CS@Se can reduce oxidative stress damage, inhibit tau hyperphosphorylation, and reduce inflammation	138
Poly(ethylene glycol) (PEG) and cetyltrimethylammonium bromide (CTAB)-modified silica nanoparticles	Catechin	Silica nanoparticles	Delivers catechins to achieve antioxidant effects and thus inhibit neurodegenerative processes	139



Table 4 (Contd.)

Name	Active drug	Carrier	Therapeutic pathways	Ref.
Iron-chelating agent/deferisirox/human serum albumin	Iron-chelating agent/deferisirox	Human serum albumin	Coupled species can inhibit apoptotic death while enhancing autophagy	140
Construct a novel nanozyme-boosted MOF-CRISPR platform (CMOPKP)	—	—	cmkpk can cross the blood-brain barrier and deliver the CRISPR activation system to precisely activate the Nrf2 signaling pathway, thereby restoring the antioxidant capacity of neurons	141
Tacrine-8-hydroxyquinoline hybrids	Tacrine/8-hydroxyquinoline	—	The tacrin-8-hydroxyquinoline heterozygote inhibited ACH-promoted $\beta$ aggregation, penetrated the central nervous system, and showed neuroprotective properties against mitochondrial free radicals	142
Citraconylation-modified poly(ethylene glycol)-poly(trimethylene carbonate) polymer (PEG-PTMC(Cit))	HNSS	FGL-NP(Cit)	FGL-NP(Cit)/HNSS can effectively repair mitochondrial dysfunction through PGC-1 $\alpha$ and STAT3 pathways, inhibit A $\beta$ deposition and tau hyperphosphorylation, and improve neuronal damage	144

glycolic acid) nanoparticles (TRNNs) significantly improve permeability across BBB models.<sup>109</sup> Molybdenum disulfide quantum dots (MoS<sub>2</sub> QDs)-macrophage membrane (MM) nanodrugs are modified with macrophage membranes (MM) and combined with NIR irradiation to effectively target the brain.<sup>110</sup> The erythrocyte membrane-camouflaged nanodrug delivery system (TR-ZRA), modified with a transferrin receptor aptamer, targets and crosses the BBB to improve the immune milieu in AD.<sup>111</sup> Traceable CNS delivery nanoformulations (RVG-NV-NPs) employ neural stem cell membranes overexpressing Lamp2b-RVG to encapsulate bexarotene and silver-gold-selenium quantum dots for CNS delivery.<sup>112</sup> These technologies utilize the advantages of cell membranes, such as biocompatibility, targeting specificity, and reduced immune response, enhancing the safety and efficacy of drug delivery.

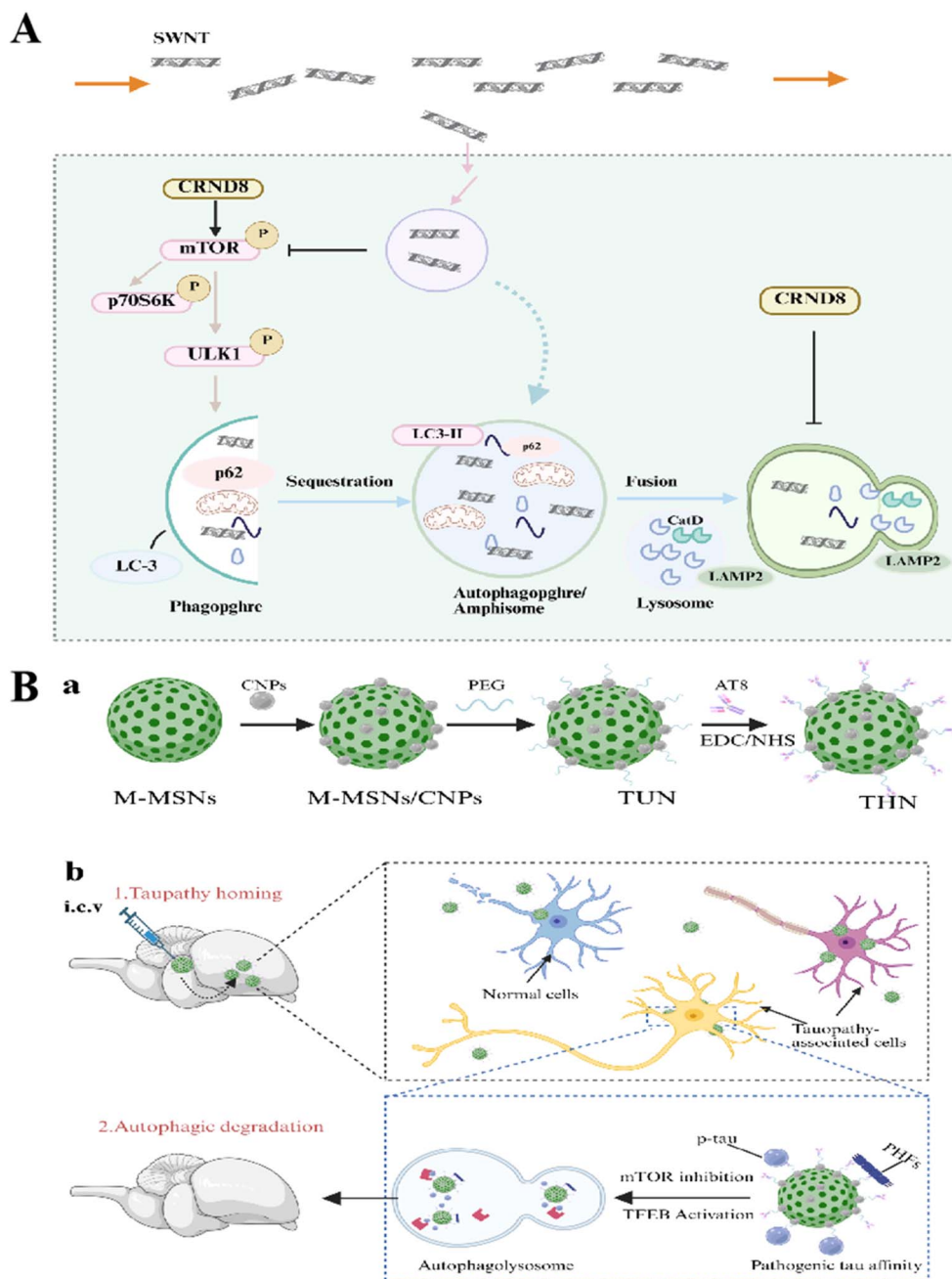
Nanocarrier systems employing specific carbon dots have also been developed. PEHA-derived CDs (PCDs) exhibit extremely low cytotoxicity compared to polyethyleneimine (PEI) and have demonstrated BBB penetration capabilities, crucial for drug delivery.<sup>113</sup> Moreover, nano C60 therapy significantly facilitates the translocation of phosphorylated CaMKII $\alpha$  from the cytoplasm to synapses in A $\beta$ 42 oligomer-treated cells and APP/PS1 mice, potentially aiding neurological delivery.<sup>114</sup> Another novel nanoassembly of indocyanine green-modified graphene quantum dots (NBGQDs-ICGs) is utilized for photodynamic therapy (PDT), inhibiting A $\beta$ 42 self-assembly and disassembling preformed fibrils, achieving BBB penetration under irradiation at 808 nm.<sup>115</sup>

Furthermore, polymeric delivery systems characterized by large surface area and strong loading capacity have garnered significant attention. A novel nano-delivery vehicle system composed of lactoferrin-conjugated (Lf-PIC@Se) micelles exhibits higher cellular uptake rates than PIC@Se micelles, successfully traversing the BBB in murine models.<sup>116</sup> PEG-PDMAEMA siRNA nanocarriers, modified with CGN and Tet1 peptides, facilitate BBB penetration and neuron-specific binding, directing siRNA specifically to brain neurons (Fig. 5A).<sup>117</sup> Chitosan nanoparticles loaded with A $\beta$  serve as a vehicle for A $\beta$ , crossing the BBB to assess performance and immunogenicity.<sup>118</sup> The SNV intelligent nanocarrier system, integrating chitosan polymers and IgG4.1 polyamine-modified F(ab') fragments, penetrates the BBB to target cerebrovascular amyloid formations in AD and cerebral amyloid angiopathy (CAA).<sup>119</sup>

These nanotechnologies and delivery systems enhance drug delivery through various mechanisms, improving BBB permeability and addressing AD-specific pathological features, thus offering new strategies for AD treatment. Further in-depth studies into the complex pathophysiology of the human brain and a better understanding of the BBB are critical for developing novel small molecules, advanced drugs, and carriers.

### 1.6 Nanocomposites that inhibit oxidative stress

Research has shown that oxidative stress-induced mitochondrial dysfunction plays a critical role in the pathogenesis of AD. Oxidative stress arises from an imbalance between the



**Fig. 6** (A) Graphic illustration of the autophagy pathway and its impairment in CRND8 glial cells at two levels: lowered autophagy induction and lysosomal proteolytic dysfunction, which are believed to contribute to AD pathogenesis,<sup>6,27</sup> macroautophagy, hereafter referred to as autophagy, involves induction steps dependent on the inhibition of mTOR, elongation of a membrane structure (phagophore) around a substrate or a region of cytoplasm, closure of this structure to form an autophagosome, and fusion of the autophagosome with lysosomes creating an autolysosome within which autophagosomes are degraded by acidic hydrolases, yielding a lysosome. To assess autophagy, we assayed the activation state of mTOR (induction), formation, and translocation of LC3-II to autophagosomes (autophagosome formation), and autolysosomal degradation of autophagy substrates, including two autophagy related proteins, LC3-II and p62. Lysosome function is monitored by assay of cathepsin D (CatD) activation (proteolysis), CatD maturation (enzyme activation and lysosomal pH), and lysosomal acidification. The graphic depicts the sites of action of single-walled carbon nanotubes (SWNTs), internalized by endocytosis, in restoring normal autophagy function by depressing mTOR activity (asterisks) to stimulate autophagy induction and enhancing lysosomal proteolysis by increasing cathepsin activation possibly by restoring normal acidification of lysosomes (asterisks).<sup>145</sup> (B) Designed fabrication of THN with autophagy-activating capacity for AD treatment. (a) Preparation of THN. (b) Schematic illustration of THN for activating autophagy-mediated clearance of pathogenic tau in AD. THN is given via intracerebroventricular (i.c.v.) injection and can penetrate into the pathological hippocampus. THN can simultaneously target and bind to the intracellular hyperphosphorylated tau (p-tau) and/or PHFs and selectively accumulate in the tauopathy-associated cells and brain regions. Also, THN is capable of enhancing autophagic flux by concurrently inhibiting mTOR and activating TFEB, which promotes efficient clearance of pathogenic tau and thus restores tau homeostasis in the brain.<sup>146</sup>



production of reactive oxygen species (ROS) and antioxidant defenses, resulting in free radical damage to mitochondria.<sup>120</sup> Mitochondrial dysfunction initiates the production of A $\beta$  and increases tau phosphorylation. The elevated levels of A $\beta$  may augment ROS production, alter oxidative phosphorylation, and interact with mitochondrial dynamics and matrix proteins, exacerbating mitochondrial damage and creating a “vicious cycle” that ultimately leads to neuronal injury.<sup>121</sup> Consequently, therapies aimed at reducing oxidative stress and regulating homeostasis in AD have garnered increasing attention. Current reports highlight that nano-strategies developed for AD therapy target oxidative stress primarily through the delivery of anti-inflammatory agents, such as natural anti-inflammatory compounds and metal nanoparticles (as depicted in Table 4).

Plant extracts with antioxidant properties are often utilized in treating various diseases; however, practical factors such as poor solubility and the inability to target disease sites have significantly impeded further research and clinical application. In response, researchers have encapsulated various plant extracts such as resveratrol, schisandrin B, naringin, curcumin, *etc.* into novel nano-systems to achieve targeted delivery across biological barriers, while also mitigating the side effects of these extracts (Fig. 5B).<sup>31,122–137</sup> For instance, Pan *et al.* encapsulated silicristin into human serum albumin (HSA) nanoparticles to formulate silicristin-HSA nanoparticles, which exhibited superior neuroprotective and antioxidant activity compared to free silicristin, thereby enhancing its antioxidative efficacy.<sup>126</sup> Similarly, Yang *et al.* developed selenium nanoparticle/chitosan nanoparticle-loaded flower-like nano-flowers containing Res (Res@SeNPs@Res-CS-NPs) to modulate oxidative stress and inhibit A $\beta$  aggregation and tau phosphorylation.<sup>123</sup>

Certain metal particles or ions (such as cerium oxide nanoparticles, nano-selenium, Cu(II), iron ions, *etc.*) also exhibit antioxidative stress properties and therefore have been explored for antioxidative stress therapy in AD.<sup>125,137–140</sup> Among these, cerium oxide nanoparticles (CNPs) have recently emerged as therapeutic candidates for AD due to their antioxidative properties, holding potential for intranasal CNP development in experimental AD treatments.<sup>125</sup> Similarly, chondroitin sulfate nano-selenium (CS@Se) can reduce oxidative stress injury, inhibit tau hyperphosphorylation, slow AD progression, and enhance learning and memory in AD mice.<sup>138</sup>

The development of nanozyme or nanomedicine-based nano-platforms has also substantially enriched the antioxidative stress treatment landscape for AD. For example, Yang *et al.* designed and constructed an innovative nanozyme-enhanced MOF-CRISPR platform (CMOPKP) capable of maintaining redox homeostasis and rescuing the impaired AD microenvironment.<sup>141</sup> Taliyan *et al.*'s thiazolidinedione nanomedicine demonstrates potent neuroprotective effects by upregulating growth factor mRNA expression and inhibiting oxidative stress and neuroinflammation, thereby preventing neuronal damage in AD.<sup>131</sup> Additionally, multifunctional nano-platforms with multiple targeting effects, including antioxidative stress, have been developed, such as a novel tacrine-8-hydroxyquinoline hybrid that reduces A $\beta$  levels and exhibits

commendable antioxidant properties.<sup>142</sup> Wang *et al.* developed a near-infrared-II aggregation-induced emission (AIE) nanotheranostic agent for precise AD therapy, which can specifically inhibit A $\beta$  fibril formation and effectively scavenge ROS and inflammation to enhance therapeutic efficacy.<sup>143</sup> A multifunctional combinatorial peptide comprising antioxidant peptide SS31 and neuroprotective peptide S14G-Humanin (HNSS) also effectively alleviates mitochondrial dysfunction and inhibits A $\beta$  deposition and tau hyperphosphorylation.<sup>144</sup>

Although antioxidative stress therapy holds promising potential in AD research, its limitations—such as uncertain efficacy, significant side effects, and low bioavailability of antioxidants—suggest the necessity of multifaceted therapeutic strategies that incorporate interventions targeting various mechanisms to effectively tackle this complex disease.

### 1.7 Nanotechnology-based strategy targeting cellular autophagy

Autophagy is a conserved degradative process that involves the lysosomal degradation of defective proteins or organelles, thereby recycling essential components of eukaryotic cells. Depending on the distinct mechanisms by which autophagic cargo is delivered to lysosomes, autophagy is generally categorized into three types: macroautophagy, chaperone-mediated autophagy (CMA), and microautophagy.<sup>147</sup> In recent years, dysfunctional autophagy has been shown to be closely associated with AD. Initially, electron microscopy revealed an accumulation of immature autophagic vesicles and degenerating neurites in the brains of AD patients.<sup>148</sup> Moreover, the aggregation of abnormal autophagic vesicles was observed preceding the formation of amyloid plaques.<sup>149</sup> Recently, it has been identified that the expression of several autophagy-related proteins is downregulated in AD brains.<sup>150,151</sup> These findings strongly suggest that autophagy is impaired in AD and that defective autophagy contributes to AD pathogenesis. Consequently, reversing or ameliorating impaired autophagy may represent a potential therapeutic avenue for AD.

Multiple nanotherapeutic strategies targeting autophagy in AD have been reported. Li *et al.* developed an RP-1 peptide-modified reactive oxygen species (ROS)-responsive micelle (RT-NM) loaded with rapamycin or gypenoside XVII. This nanoplatform activates the entire autophagy-lysosome pathway by inducing autophagy and improving lysosomal function, thereby enhancing the degradation of neurotoxic aggregates and inflammasomes, promoting the phagocytosis of A $\beta$ , and consequently ameliorating memory deficits in 3  $\times$  Tg-AD transgenic mice.<sup>152</sup> However, existing mitophagy inducers are often constrained by toxicity and inadequate brain accumulation. To address this, researchers developed a nanoscopic mesenchymal stem cell-derived extracellular vesicle platform (MSC-EVs-SHP2), utilizing high expression of tyrosine phosphatase-2 (SHP2) for AD treatment. These vesicles can traverse the BBB, facilitating SHP2 delivery to the brain, and significantly inducing neuronal mitophagy.<sup>153</sup>

Additionally, hyperphosphorylation and aggregation of tau protein are closely related to autophagic defects in neurons.



Table 5 Summary table comparing the comprehensive performance of different nanocarriers

	Liposomes	Polymeric microspheres	Dendrimers	Exosomes	MOFs
Size range (nm)	50–200	100–1000	2–15	30–150	50–300 (tunable)
Zeta potential (mV)	–10 to –40	–15 to –30	+5 to +30	–10 to –25	–20 to +20
Main administration routes	Intravenous and intranasal	Intramuscular, subcutaneous implantation, and sustained-release devices	Intravenous and intranasal	Intravenous, intranasal, and oral	Intravenous and oral
BBB	Moderate	Weak	Strong	High	Moderate
Therapeutic efficacy in AD models	Delivery of anti-A $\beta$ antibodies, siRNA; and reduction of amyloid plaques	Sustained release of cholinesterase inhibitors; cognitive improvement	Inhibition of A $\beta$ aggregation and modulation of neuroinflammation	Delivery of neurotrophic factors and miRNA; neuroprotective effects	High drug-loading capacity; antioxidant and metal-chelating functions
Biocompatibility	High	Moderate	Moderate	Very high	Low
Immunogenicity	Low	Moderate	Moderate to high	Very low	Moderate to high
Clearance mechanisms	Primarily <i>via</i> MPS uptake; renal filtration for smaller particles	Slow degradation with MPS involvement	Renal clearance and MPS uptake	Endogenous metabolic pathways and partial hepatic processing	Hepatic and renal clearance
Potential organ toxicity	Low	Hepatic and renal burden	Neurotoxicity risk	Very low	High risk

Researchers reported a tauopathy-homing nanostructure (THN) that binds and clears pathological tau, selectively accumulating in affected cells, thereby rescuing neuronal viability and cognitive function in AD rats (Fig. 6B).<sup>146</sup> Similarly, polyethylene glycol (PEG)-ceramide nanomicelles synthesized by Yin *et al.* can induce tau degradation through autophagy.<sup>154</sup> Moreover, simple functionalized single-walled carbon nanotubes (SWNTs) can facilitate the elimination of autophagic substrates by reversing the abnormal activation of mTOR signaling and lysosomal proteolytic defects, thereby restoring normal autophagic processes (Fig. 6A).<sup>145</sup> These studies offer new methodologies and perspectives for AD therapy. However, the current paucity of research on autophagic mechanisms in AD and the lack of clinical trials limit the further development of nanotherapeutic strategies.

## 2 Discussion

Currently, the majority of therapeutic drugs used in clinical trials for AD are mostly based on monoclonal antibody-based biological agents and small molecule inhibitors. This transformation gap highlights the ongoing challenges in scalability, long-term biological safety assessment, and regulatory standardization of nanocarrier systems.<sup>155</sup>

Firstly, the manufacturability of nanotherapeutics represents a primary bottleneck in their clinical translation. Laboratory-scale synthesis methods employed during preclinical development are inherently difficult to scale up directly to Good Manufacturing Practice (GMP)-compliant production.<sup>9,23</sup> For instance, lipid-based nanoparticles are prone to inter-batch variability in particle size distribution and drug encapsulation efficiency during scale-up, leading to inconsistent pharmacological activity. The field is increasingly exploring continuous manufacturing platforms, including microfluidic technologies, to enhance reproducibility and process efficiency.<sup>31</sup>

Secondly, regulatory evaluation of nanotherapeutics remains hampered by the absence of harmonised global standards.<sup>82,156</sup> Regulatory bodies such as the U.S. Food and Drug Administration (FDA) mandate comprehensive physicochemical characterisation, but current analytical techniques, such as dynamic light scattering, may lack accuracy in complex biological matrices. Moreover, long-term toxicity assessment necessitates the development of specialised models, as conventional animal studies often fail to reliably predict risks associated with cerebral bioaccumulation.<sup>95</sup> Table 5 summarizes the comparisons of various properties of different types of nanodelivery materials.

Additionally, the development cost of nanotherapeutics substantially exceeds that of traditional therapeutics. Custom synthesis of A $\beta$ -targeted antibody-nanoparticle conjugates, for example, may incur per-batch costs reaching several million U.S. dollars. Although innovative delivery routes, such as intranasal administration, may partially alleviate costs, the overall economic feasibility remains a significant challenge.<sup>98</sup> Addressing these barriers demands interdisciplinary collaboration: the establishment of standardised manufacturing platforms, the creation of international regulatory frameworks, and the investigation of cost-effective alternative raw materials. Only through overcoming these translational hurdles can nanomedicines progress from bedside innovation to bedside application in the treatment of AD.

Finally, although rodent models provide insights into mechanisms, their reproducibility in human blood-brain barrier physiological characteristics and disease heterogeneity is limited, which further complicates the extrapolation of results to the clinical setting.<sup>96</sup> Therefore, we believe that although nanomedicine brings transformative potential for AD treatment, its path to clinical application is still limited by scientific and operational obstacles.<sup>155</sup> To bridge this gap,



interdisciplinary collaboration, unified feature detection standards, and reliable translational frameworks are needed to convert promising preclinical research results into nanotherapies with clinical application value.

### 3 Perspectives and conclusions

Alzheimer's disease, as a neurodegenerative disorder, remains without a definitive cure despite notable advancements in therapeutic research over recent years. Over the past few decades, researchers have successfully developed various nanomaterials for drug delivery and targeted therapy that not only traverse the blood–brain barrier but also demonstrate significant therapeutic efficacy in animal models. However, despite the encouraging progress in nanoparticle therapies for AD, several challenges and limitations persist.

Firstly, while nanotherapeutics for AD have demonstrated considerable promise in traversing the BBB and selectively targeting pathological proteins, challenges pertaining to biodistribution, bioaccumulation, and clearance remain pivotal obstacles to clinical translation. The accumulation of nanomaterials within cerebral tissues may lead to irreversible neurotoxic effects. Similarly, biomimetic nanocarriers may elicit chronic inflammatory responses due to inherent immunogenicity, thereby accelerating neuronal degeneration. Furthermore, the efficiency of nanotherapeutic clearance is profoundly influenced by BBB integrity. Heterogeneity in nanoparticle size contributes to inconsistent clearance kinetics. These findings underscore the necessity of optimising nanocarrier design to balance targeted delivery with safe elimination profiles. Future strategies should prioritise biodegradable formulations, stimuli-responsive release mechanisms, and real-time monitoring of biodisposition to mitigate long-term risks and enhance the therapeutic index in neurodegenerative interventions.

Secondly, the *in vivo* distribution, metabolism, and excretion mechanisms of nanoparticles remain incompletely understood. Looking ahead, key areas for the development of novel nanoparticle therapeutics include the optimized design of nanoparticles, personalized therapeutic regimens, combination treatment strategies, as well as preclinical and clinical research. In summary, nanotechnology holds the potential to offer safer and more efficacious therapeutic options for AD patients in the future.

### Conflicts of interest

The authors declare no competing interests.

### Data availability

This study was carried out using publicly available data from Pubmed.

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