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Perspective

Advancing Nanomaterial-Based Strategies for Alzheimer's Disease: A Perspective

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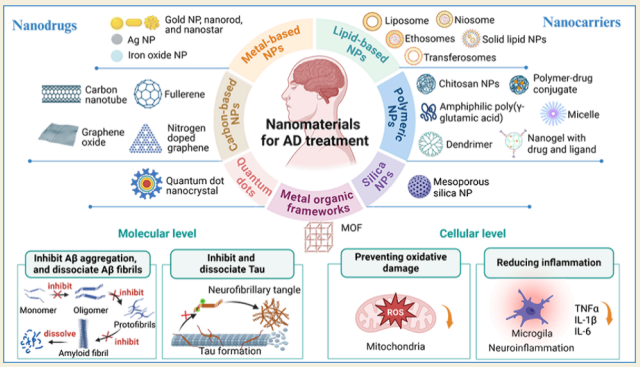
ABSTRACT: Alzheimer's disease (AD) is a complex neurodegenerative disorder and the most common cause of dementia. By 2050, the number of AD cases is projected to exceed 131 million, placing significant strain on healthcare systems and economies worldwide. The pathogenesis of AD is multifactorial, involving hypotheses/mechanisms, such as amyloid-β (Aβ) plaques, tau protein hyperphosphorylation, cholinergic neuron damage, oxidative stress, and inflammation. Despite extensive research, the complexity of these potentially entangled mechanisms has hindered the development of treatments that can reverse disease progression. Nanotechnology, leveraging the unique physical, electrical, magnetic, and optical properties of nanomaterials, has emerged as a promising approach for AD treatment. In this Perspective, we first outlined the major current pathogenic hypotheses of AD and then reviewed recent advances in nanomaterials in addressing these hypotheses. We have also discussed the challenges in translating nanomaterials into clinical applications and proposed future directions, particularly the development of multifunctional and multitarget nanomaterials, to enhance their therapeutic efficacy and clinical applicability in AD treatment.



1. INTRODUCTION

Alzheimer's disease (AD) is one of the most common neurodegenerative disorders, primarily characterized by memory impairment, confusion, and cognitive decline. As the leading cause of dementia, AD accounts for 60−80% of all dementia cases worldwide. It is estimated that 10.9% of individuals aged 65 and above have AD, with the risk increasing monotonically with age.[1] Among those over 85 years old, the prevalence rises to 33.4%, and the annual incidence is estimated at 7.6%. As the global population ages, the incidence of AD is expected to escalate sharply, imposing a significant burden on healthcare systems and patient families.

The pathogenesis of AD is highly complex and remains incompletely understood.[2] Various hypotheses have been proposed to explain its onset, including the Aβ cascade hypothesis,[3] Tau hypothesis,[4] cholinergic hypothesis,[5] mitochondrial cascade hypothesis,[6] neuroinflammation hypothesis,[7] metal ion hypothesis,[8] oxidative stress hypothesis,[9] calcium homeostasis hypothesis,[10] neurovascular hypothesis,[11] and others.[12] These frameworks provide valuable insights into the molecular, cellular, neural, and physiological dimensions of AD pathology. Emerging evidence, however, indicates that AD may result from a multifactorial disruption of intracellular homeostasis, driven by intricate interactions among these pathways.[13] Consequently, effective therapeutic strategies may require a multitargeted approach that addresses key pathologies such as Aβ, tau protein, neuroinflammation, vascular dysfunction, and lifestyle factors to slow or halt disease progression in a more comprehensive way.

Given the complexity of AD's pathology, developing effective treatments remains a significant challenge. To date, the U.S. Food and Drug Administration (FDA) has approved only seven drugs for AD (Figure 1). Among these, donepezil, rivastigmine, galantamine, memantine, and namzaric have been widely used to manage symptoms but do not alter the disease's progression. More recently, monoclonal antibodies such as donanemab[14] and lecanemab[15] have been approved to reduce Aβ plaques and slow cognitive decline in the early stages of AD. However, these therapies are not suitable for all patients, carry risks of side effects such as headaches, nausea, and infusion reactions, and remain financially inaccessible for many

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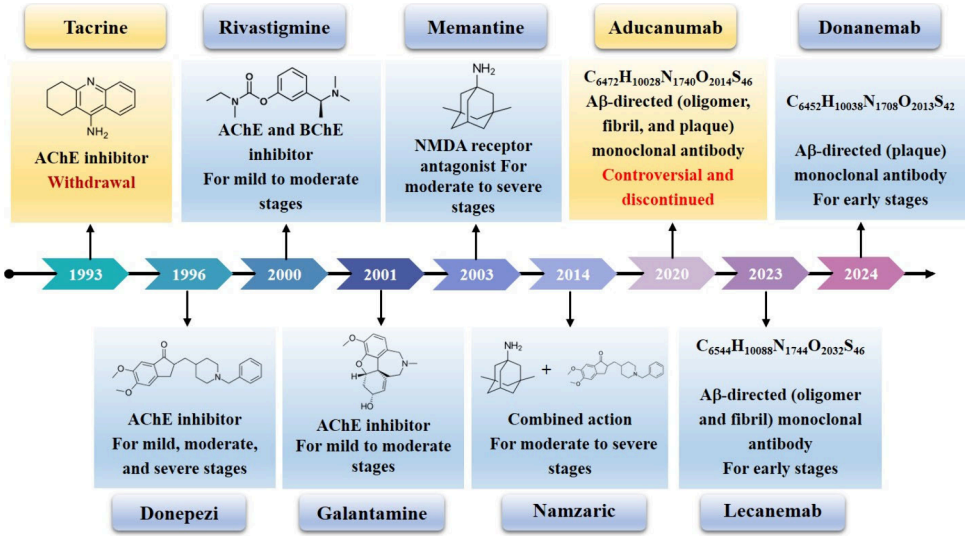

Figure 1. FDA-approved medications for the treatment of Alzheimer's disease.

due to their high costs. A survey by Cummings et al. reported that, as of January 1, 2024, 127 drugs are in clinical trials for AD, with 41% classified as small molecules and 34% classified as biologics. Despite ongoing efforts, only 32 candidates have progressed to Phase III trials, underscoring the significant hurdles in advancing new therapeutic options.[16]

Meanwhile, rapid developments in nanotechnology have provided an unprecedented opportunity to consummate the treatment of AD.[17,18] Nanomaterials possess unique properties, including physicochemical stability, high surface-area-to-volume ratios, and customizable fabrication and functionalization, making them ideal candidates for use as both therapeutic agents and drug carriers. For instance, metal-based nanoparticles (MNPs),[19] carbon-based nanoparticles (CNPs),[20−22] and quantum dots (QDs)[23] can target Aβ or Tau proteins to inhibit aggregation or promote clearance. Lipid-based nanoparticles (LNPs), polymeric nanoparticles (PNPs), mesoporous silica nanoparticles (MSNs), and metal−organic frameworks (MOFs) demonstrate high selectivity and efficiency in interacting with biological systems at the molecular level.[18,24] The dual functionality of nanomaterials as both carriers and active therapeutic agents positions them as a promising and transformative strategy for advancing AD treatment.

2. COMPLEXITY AND DIVERSITY OF AD PATHOGENESIS

In 1906, Alois Alzheimer presented the first signature case and pathological features of the disease. Later, in 1910, his coworker Emil Kraepelin named the disease in honor of his achievements. However, it was not until 1963 that Robert Terry and Michael Kidd revived their interest by performing electron microscopy of neuropathological lesions.[25,26] Since then, over half a century of research has been dedicated to elucidating the pathological features and mechanisms of AD and developing therapeutic approaches.

AD is recognized as a multipathological disease with two primary pathological hallmarks: the extracellular accumulation of Aβ in senile plaques and the intracellular formation of neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein.[2,27−29] Various hypotheses have been proposed to elucidate the pathogenesis of AD (Figure 2). These hypotheses suggest potential mechanisms underlying

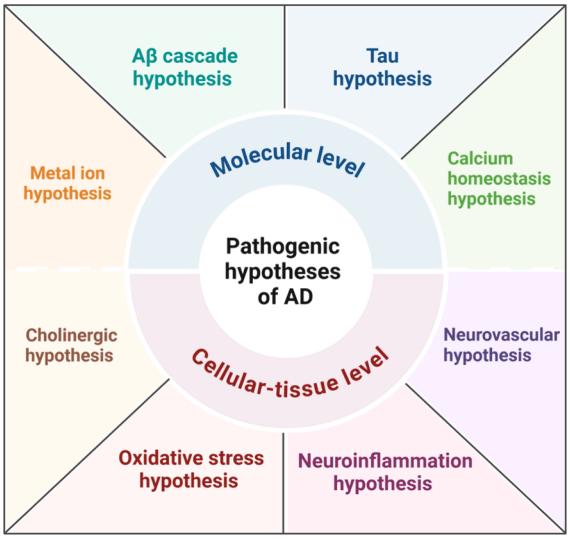

Figure 2. Current major pathogenic hypotheses of AD.

the formation of amyloid plaques, neurofibrillary tangles, and neuronal cell death across the different biological scales, from the molecular level to the cellular-tissue level. Among these, the amyloid cascade hypothesis remains the most widely accepted and continuously refined in recent research.[30,31] This framework posits that the cleavage of amyloid precursor protein (APP) by β- and γ-secretases produces peptides of approximately 39−43 amino acids. These peptides initially aggregate into neurotoxic soluble oligomers, with Aβ_{42} oligomers demonstrating relatively high neurotoxicity.[32] Impaired clearance of these soluble oligomers leads to synaptic damage, oxidative stress, neuroinflammation, and tau protein hyperphosphorylation, ultimately resulting in the formation of neurofibrillary tangles, apoptosis, and other downstream pathological processes. This cascade is believed to act as an important trigger for further molecular and cellular damage. At the molecular level, AD pathology primarily involves Aβ and tau proteins, while at the cellular level, mitochondrial oxidative stress and microglia-driven neuroinflammation are the predominant contributors. Therefore, current nanomaterial-based therapeutic strategies for AD mainly target these four

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key pathological factors. In the following section, we provide a concise overview of the prevailing hypotheses on AD, with some discussions on the progress of therapeutic research targeting these mechanisms.

2.1. Cholinergic Hypothesis

The cholinergic hypothesis, first proposed by Peter Davies and A. J. F. Maloney in 1976,[5] is the earliest theory on the pathogenesis of AD and serves as the foundation of most current AD drugs. Cholinergic synapses are ubiquitous in the human central nervous system, with cholinergic transmission playing a crucial role in memory, learning, attention, and other cognitive functions. The cholinergic hypothesis suggests that AD-affected brains exhibit reduced production and transportation of the neurotransmitter acetylcholine.[33,34]

Acetylcholinesterase inhibitors (AChEIs) alleviate cognitive impairment in AD patients by preventing acetylcholine degradation. Tacrine, velnacrine, and physostigmine, classified as first-generation AChEIs,[35] were withdrawn from the market due to their high rates of potential drug interactions and serious side effects. In response, second-generation AChEIs, including donepezil, rivastigmine, and galantamine, were rapidly developed and subsequently approved by the FDA for treating AD. However, evidence supporting the efficacy and effectiveness of AChEIs remains limited, particularly in cases of severe dementia, advanced age, and long-term treatment.[36,37]

2.2. Amyloid Cascade Hypothesis

The amyloid cascade hypothesis (ACH), first proposed in 1992 by Hardy and Higgins,[3] has evolved over three decades into the leading theory for understanding AD pathogenesis.[38] This hypothesis suggests that the accumulation of Aβ is the primary event triggering a series of molecular processes, including the formation of hyperphosphorylated tau aggregates and the activation of neuronal death pathways, ultimately resulting in dementia. Extensive studies have validated the cytotoxic effects of Aβ, identifying prefibrillar Aβ oligomers as the most toxic species.[39,40] Consequently, the ACH suggests that reducing Aβ accumulation in the brain could slow or halt disease progression.

Current AD treatments inspired by the ACH can be categorized into four main approaches: (1) β- and γ-secretase inhibitors to reduce Aβ production; (2) antiaggregation agents, including metal chelators, to prevent Aβ aggregation; (3) protease-modulating drugs to enhance Aβ clearance; and (4) immunotherapies, particularly monoclonal antibodies targeting pathological Aβ deposits. The recent approval of monoclonal antibodies, including aducanumab,[41] lecanemab, and donanemab, has brought renewed optimism to the field. Despite the improvements in some neurocognitive test scores, the actual clinical impact of these therapies remains limited, highlighting unresolved challenges and potentially overlooked factors in achieving meaningful therapeutic success.[42]

2.3. Tau Hypothesis

In 1996, Braak et al. identified intracellular NFTs, composed of tau proteins, as a defining pathological feature of AD.[43] According to the tau propagation hypothesis, these NFTs are formed through the aggregation of abnormally phosphorylated tau proteins, resulting in microtubule depolymerization and thus disrupting signal transmission within and between neurons.[44−46] The tau propagation hypothesis and the amyloid cascade hypothesis are widely regarded as the two most accepted pathogenic mechanisms of AD, with growing evidence suggesting crosstalk between them.[47,48] This has given rise to the concept that Aβ may act as the "trigger", while tau serves as the "bullet" driving neurodegeneration.[49]

Various tau-based therapeutic strategies have been proposed, including reducing tau expression, inhibiting tau aggregation, stabilizing microtubules, targeting tau protein modifications, and promoting tau clearance through immunotherapy.[50−52] Several drugs such as TRx0237[53] (a tau aggregation inhibitor), ACI-35,[54] and AADvac1[55] (active tau-targeted vaccines) are still being evaluated in clinical trials. Tau-directed therapies will inevitably face challenges similar to those presently encountered in Aβ-targeted trials and will require ongoing research and development efforts, including the combination of tau and Aβ-targeting therapies, optimizing antibody design, and developing new delivery systems.[50]

2.4. Oxidative Stress Hypothesis

In 1997, Mark A. Smith and colleagues provided the first compelling evidence linking oxidative stress to AD, laying the foundation for the oxidative stress hypothesis.[56] This hypothesis suggests that factors such as metal accumulation, overexpression of related enzymes, and mitochondrial dysfunction contribute to the production of excessive reactive oxygen species (ROS), overwhelming the brain's antioxidant defenses and leading to oxidative imbalance. The resulting damage to neuronal membranes, proteins, and nucleic acids ultimately causes neuronal cell death.[57−59] Oxidative stress also plays a key role in various AD-related mechanisms, including inflammation in the amyloid cascade, NFTs, and metal ion hypotheses.[59]

Given these connections between oxidative stress and other AD mechanisms, antioxidants have emerged as promising therapeutic agents. Animal studies have shown positive results, but the efficacy of antioxidants in clinical trials remains inconclusive.[60] Future research should focus on optimizing dosage regimens and initiating antioxidant therapy early in the disease's progression to potentially enhance therapeutic outcomes.[61] Additionally, further investigations into the interplay between Aβ and oxidative stress,[62] as well as their role in the sequence of AD pathogenesis,[63,64] are essential for advancing our understanding and treatment of the disease.

2.5. Neuroinflammation Hypothesis

Since the 1980s, studies have reported immune-related proteins and cells near Aβ plaques.[65] Initially, neuroinflammation was considered as a secondary response, followed by amyloid cascade and NFTs. However, growing evidence has suggested that neuroinflammation can be a causative factor in AD pathogenesis, as well. Alterations in the immune system have been observed even before the onset of AD symptoms, implying that inflammation may independently drive pathological cascades while also interacting with amyloid and tau pathways, creating a vicious cycle.[66,67]

However, the effectiveness of nonsteroidal anti-inflammatory drugs (NSAIDs, microglia modulators) in treating AD remains inconclusive,[68−70] indicating again AD is a complex multipathological disease. Numerous other drugs targeting inflammation-related receptors, signaling pathways, and pro-inflammatory cytokines are currently in clinical trials.[70] A deeper understanding of the complex mechanisms underlying neuroinflammation could reveal novel therapeutic targets, enabling the development of more effective treatments to mitigate AD-associated morbidity.

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2.6. Metal Ion Hypothesis

The metal ion hypothesis was proposed by Bush et al., who first established a link between zinc (Zn) and Aβ in 1994.[8] Since then, the potential relationship between biometals and AD has been intensively studied.[71,72] The homeostasis of metal ions, particularly Zn and copper (Cu), is crucial to maintaining normal brain functions. Abnormal deposition or distribution of these metal ions can induce oxidative stress. Metal ion imbalances and oxidative stress, either independently or synergistically, promote Aβ overproduction and tau hyperphosphorylation. Additionally, an imbalance of metal ions can disrupt organelles directly or indirectly, leading to endoplasmic reticulum stress, mitochondrial dysfunction, and autophagy impairment. These disruptions exacerbate the accumulation of Aβ and tau, further impairing the synaptic function. Moreover, the alterations induced by metal ion imbalances can worsen their misdistribution and deposition, creating a vicious cycle with Aβ/tau abnormalities. Ultimately, this cycle drives chronic neurodegeneration and cognitive deficits.[73]

The potential of using metal chelators to regenerate the normal trafficking of metal ions has been considered a promising strategy to reduce the redox stress that is lethal for neurons.[74−77] However, most attempts to use metal chelators as therapeutic agents have been limited to existing molecules available on the shelves. Very few chelators have resulted from a rational design aiming to create drugs with a safety profile and the ability to cross the blood−brain barrier (BBB) after an oral administration.

2.7. Calcium Homeostasis Hypothesis

The calcium homeostasis hypothesis, first proposed by Mattson et al. in 1992,[10] suggests that disruptions in cellular calcium ion (Ca^{2+}) balance play a critical role in the progression of AD. Calcium affects AD progression through four main pathways: (1) excessive calcium influx disrupts homeostasis, causing neuronal damage and dysfunction; (2) increased intracellular calcium levels promote Aβ deposition;[78] (3) calcium overload leads to abnormal phosphorylation of tau, impairing its binding to microtubules and resulting in neurofibrillary tangles;[79] and (4) disrupted calcium homeostasis impairs synaptic plasticity.

Ca^{2+} antagonists are the main clinically developed AD therapeutic drugs based on calcium homeostasis.[80] Curcumin, for example, acts as an intracellular calcium inhibitor and has been shown to protect astrocytes from oxidative stress and white matter from hypoxia, thereby reducing apoptosis and mitigating glutamate-induced neurotoxicity.[81] Aducanumab has also demonstrated its ability to alleviate calcium overload in previous studies.[82] Although preclinical research has shown promise for calcium modulators as potential AD treatments, clinical trials in humans have yielded mixed results.[83] Additionally, given the essential role of calcium in numerous cellular processes, the use of calcium modulators in AD treatment is complicated by potential side effects.

2.8. Neurovascular Hypothesis

The vascular hypothesis of AD was first proposed by de la Torre and Mussivand in 1993,[84] which highlights the critical role of blood vessels in the pathological pathways leading to neuronal damage and dementia. According to this hypothesis, disruption of the BBB and reduction of cerebral blood flow are critical factors linking vascular risk to neurodegeneration.[85] BBB disruption promotes the accumulation of Aβ and impairs Aβ clearance mechanisms, while decreased cerebral blood flow enhances APP expression and β-secretase activity, leading to increased Aβ production. Consequently, cerebral hypoperfusion contributes to Aβ accumulation through a positive feedback mechanism; in turn, Aβ accumulation exacerbates vascular dysfunction, resulting in inflammation and oxidative stress.

Many factors can alter the neurovasculature, subsequently influencing the onset and progression of AD. Hyperlipidemia and hyperglycemia are among the most significant factors.[86,87] Cholesterol-lowering statins, the antihypertensive drug ramipril, and nonsteroidal anti-inflammatory drugs are considered promising for AD prevention and treatment.[88−90] Nonetheless, the failure of clinical trials targeting the neurovascular hypothesis and related models indicates that these hypotheses alone may not fully explain the complex etiology of AD.[91−94]

Overall, while existing hypotheses and therapeutic strategies have laid a foundation for AD research, a comprehensive understanding of the disease's complex etiology is still lacking. Future research will need to focus on unraveling these intricate and often entangled mechanisms and developing more effective, multitarget treatments to improve outcomes for AD patients.

3. TYPES OF NANOMATERIALS FOR AD TREATMENT

With the advent of nanotechnology, the wide use of nanomaterials as a front-line tool in biomedical sciences is widely recognized.[95,96] In the context of neurodegenerative diseases, the utilization of nanomaterials is particularly appealing due to their size range of 1 to 100 nm, which enables efficient BBB penetration.[97,98] As mentioned earlier, nanomaterials developed for AD primarily target Aβ and tau proteins at the molecular level while also mitigating oxidative stress and neuroinflammation at the cellular level. Functionally, nanomaterials are classified into two main categories: nanodrugs that directly treat target diseases and nanocarriers that deliver conventional drugs.[99,100] Nanodrugs interact directly with these targets via their intrinsic physicochemical properties and typically include MNPs, CNPs, and QDs. Specifically, inorganic metals and their oxides, such as gold (Au), silver (Ag), and cerium oxide (CeO_2) NPs, exhibit photothermal/magnetothermal effects as well as antioxidant capabilities,[101] enabling direct intervention in AD pathogenesis by modulating Aβ aggregation, tau pathology, and mitochondrial oxidative stress. Furthermore, CNPs and their derivatives have been shown to prevent the aggregation of Aβ monomers into toxic fibrils through hydrophobic interactions, hydrogen bonding, and salt bridge formation, facilitated by surface-functionalized modifications.[21,22] QDs, with sizes comparable to Aβ and tau proteins, are frequently employed as direct nanomedicines.[102,103] Their unique optical properties, arising from quantum confinement effects, further enhance their utility for AD diagnosis. Nanocarriers have been developed to address challenges such as poor BBB penetration, low targeting specificity, and systemic toxicity associated with AD drugs like donepezil. These nanocarriers enhance drug stability and targeting by encapsulating therapeutic agents within the nanomaterials. Typical nanocarriers include amphiphilic polymers and porous materials. Amphiphilic polymers often include lipid-based liposomes, ethosomes, and other high-molecular-weight compounds, such as chitosan and γ-polyglutamic acid NPs. Porous materials typically include MSNs and MOFs. These nanomaterials facilitate drug transport across the BBB, offering advantages such as high

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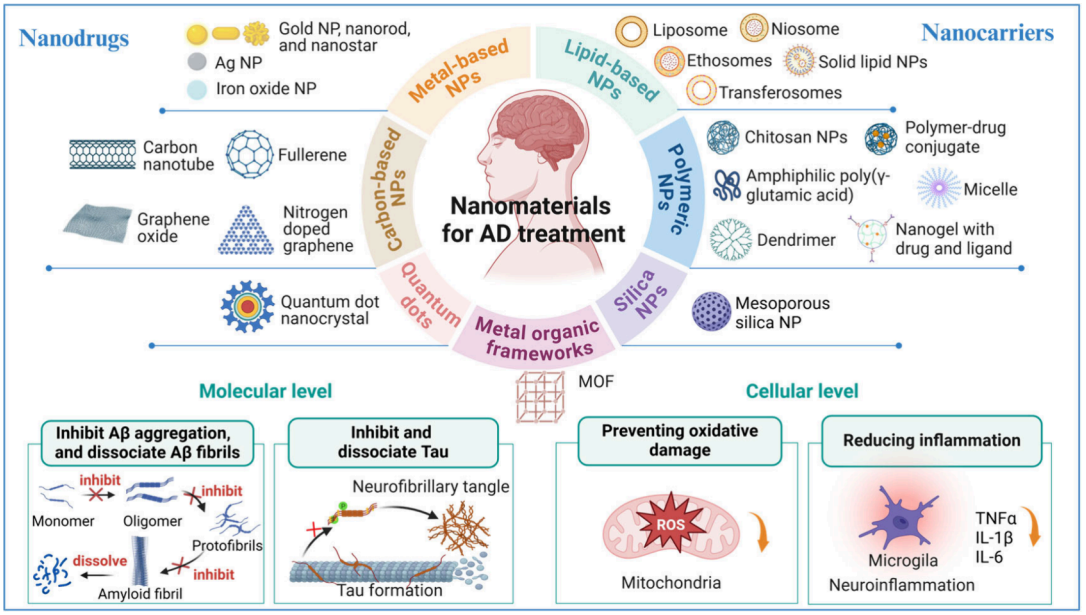

Figure 3. Nanomaterials in the treatment of AD. The upper section showcases various nanomaterials used in AD treatment, such as metal-based nanoparticles (MNPs), carbon-based nanoparticles (CNPs), quantum dots (QDs), metal−organic frameworks (MOFs), silica NPs, polymeric nanoparticles (PNPs), and lipid-based nanoparticles (LNPs). The bottom part illustrates the key mechanisms of action involving the inhibition of Aβ aggregation, clearance of fibrils, inhibition and dissociation of tau aggregates, reduction of oxidative stress, and modulation of neuroinflammation. The diagram was created by using BioRender.

drug-loading capacity, prolonged circulation, controlled release, and site-specific targeting. For example, exogenous oxytocin (OT) can inhibit microglial activation and reduce neuroinflammation by suppressing the release of pro-inflammatory factors from microglia.[104,105] However, its short half-life in the bloodstream and challenges in long-term nasal administration limit its therapeutic efficacy in AD. To address this, Ye et al. designed angiopep-2-modified chitosan nanogels for OT delivery, enabling BBB penetration via intravenous injection and sustained OT release.[106] This targeted strategy effectively reduced neuroinflammation and microglial activation in APP/PS1 mice by modulating the ERK/p38 MAPK and COX-2/iNOS NF-κB pathways, ultimately alleviating cognitive deficits and delaying hippocampal atrophy. Certain nanomaterials, such as MOFs, possess dual functionality as both nanodrugs and nanocarriers. MOFs can directly bind and sequester Aβ through their porous structures, preventing toxic aggregation, while also serving as efficient drug delivery platforms for anti-AD agents.[107,108] Overall, nanomaterials offer a versatile and promising approach to AD treatment, overcoming the limitations of conventional therapeutics by acting through both direct molecular interactions and enhanced drug delivery systems. Figure 3 illustrates a range of nanomaterials employed in AD treatment. In the following section, we discuss the unique characteristics of each nanomaterial, their specific applications in AD treatment (summarized in Table 1), and the major challenges hindering their clinical translation. As this is intended for a short perspective rather than a comprehensive review, we have limited the discussion to key aspects of the nanomaterials and therapeutics involved.

3.1. Metal-Based Nanoparticles (MNPs)

The use of MNPs in nanomedicine for AD treatment has become an increasingly promising area of research. MNPs, including pure metals and their oxides such as Au, Ag, platinum (Pt), iron oxide, and CeO_2, typically range in size from 1 to 100 nm.[109] These NPs offer significant advantages in addressing AD, particularly their ability to cross the BBB,[110] a key obstacle in neurodegenerative disease treatment. Moreover, MNPs exhibit enhanced bioavailability, stability, biocompatibility, and target specificity,[111] making them highly promising candidates for therapeutic applications. Additionally, their unique physicochemical properties—such as low Gibbs free energy, large surface area, and multivalency—further enhance adsorption capacity, improve biological interactions, and facilitate efficient coupling with proteins or biomolecules.[112]

Studies have demonstrated the potential of MNPs in modulating AD pathology through various mechanisms, including inhibiting and redirecting Aβ fibrillization, preventing tau protein aggregation, reducing inflammation, and combating oxidative stress.[101] Among MNPs, gold nanoparticles (AuNPs) stand out due to their excellent biocompatibility, ease of functionalization, and ability to cross the BBB, making them effective nanochaperones for Aβ modulation. For instance, Lu et al. reported that D- and L-glutathione (GSH)-stabilized AuNPs functionalized with an anti-NLRP3 antibody reduced Aβ aggregation and degraded intracellular NLRP3, preventing microglial senescence and enhancing Aβ fibril clearance in AD treatment.[113] Additionally, Zhang et al. developed Au nanoclusters (AuNCs) modified with Cys-Arg (CR) dipeptides, called $Au_{23}(CR)_{14}$, which effectively dissolve exogenous mature Aβ fibrils into monomers and restore Aβ peptides to their natural unfolded state.[114] Notably, $Au_{23}(CR)_{14}$ also dissolved endogenous Aβ plaques in brain slices from transgenic AD model mice. Beyond Aβ modulation, AuNPs exhibit anti-inflammatory and antioxidant properties. Tramontin et al. demonstrated that AuNPs treatment prevented cognitive impairment, regulated mitochondrial function, reduced oxidative stress, and alleviated neuroinflammation in the hippocampus and cortex.[115] In addition

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Table 1. Nanomaterials for AD Target Treatment (Only *in Vivo*/*Vitro* Study Mentioned Here)

Types	Name	Modification/Loading	Size (nm)	Targeted Pathogenesis	Molecular mechanisms and Therapeutic Efficacy	*In vivo*/*In vitro*	ref
Metal-based NPs (MNPs)	AuNPs	L3.3 and D3.3	L- and D-glutathione (GSH)	3.3	Aβ	Inhibit aggregation of Aβ_{42} and cross the BBB without noticeable toxicity	*In vivo*/*In vitro*	Hou et al., 2020[197]
	AuNPs	D- and L-NP-aNLRP3	L- and D-GSH, conjugated with anti-NLRP3 antibody	2.8 ± 0.4	Aβ	Inhibit Aβ aggregation and degraded intracellular endogenous NLRP3 inflammasomes to prevent microglial senescence	*In vivo*/*In vitro*	Lu et al., 2024[113]
	Au nanocluster	$Au_{23}(CR)_{14}$	Cys-Arg (CR) dipeptide	1.6 ± 0.5	Aβ	Restores fibril Aβ's unfolded state and dissolves endogenous Aβ plaques	*In vivo*/*In vitro*	Zhang et al., 2020[114]
	Au nanorods + Ceria	KLVFF@Au-CeO_2 (K-CAC)	KLVFF peptide	100	Aβ, oxidative stress	Inhibit Aβ monomers aggregation, dissociate Aβ fibrils, and scavenge ROS	*In vivo*/*In vitro*	Ge et al., 2022[118]
	Ag-doped $CuBi_2O_4$	KLVFF-Ag:$CuBi_2O_4$	KLVFF peptide	1 μm (thickness)	Aβ	Disassemble toxic Aβ assemblies into nontoxic, small soluble species	*In vitro*	Heo et al., 2020[198]
	Ceria NPs	TPP-ceria	DSPE-PEG-NH_2-TPP	11−22	Oxidative stress	Scavenge mitochondrial ROS, reduce oxidative stress	*In vivo*/*In vitro*	Kwon et al., 2016[117]
	MnO_2 NPs	Ab-TP-MDNPs	Anti-Aβ antibody and BBB-crossing terpolymer	118	Aβ, oxidative stress, neuroinflammation, vascular dysfunction	Reduce hypoxia, neuroinflammation, and oxidative stress ultimately leads to alterations in vascular abnormalities, lymphatic dysfunction, and Aβ accumulation	*In vivo*/*In vitro*	Park et al., 2023[119]
	Iron oxide NPs	MNPs-DP	D-TLKIVWC peptide (7-DP)	/	Tau	Prevent tau aggregation, dissolves existing tau aggregates	*In vivo*/*In vitro*	Hou et al., 2024[199]
	Palladium nanocluster	NGF-WP5⊃Cys@Pd NCs (NWP)	Nerve growth factor (NGF), carboxyl pillars[5]arenes (WP5)	220	Aβ, oxidative stress, neuroinflammation	Reduce the Aβ burden, relieve oxidative stress and neuroinflammation	*In vivo*/*In vitro*	Yuan et al., 2023[200]
	Mesoporous silica NPs	CICe@M-K	CKLVFFAED peptide, CeO_2 NPs, Cur, IR780	∼100	Aβ, oxidative stress	Inhibiting Aβ aggregation and scavenge reactive oxygen species	*In vivo*/*In vitro*	Wang et al., 2024[187]
	Mesoporous silica NPs	MSN-BBR-L lipid	Berberine-loaded, lipid coating	80−100	Aβ, AChE	Inhibit AChE activity, prevent Aβ fibrillation, reduce malondialdehyde levels, and decrease BACE-1 levels	*In vivo*/*In vitro*	Singh et al., 2021[188]
Silica NPs	Mesoporous silica NPs + cerium oxide	bMSNs@Ce-1F12	Anti-Aβ_{42} antibody 1F12 and RVG29	110	Aβ, oxidative stress	Inhibit Aβ_{42} misfolding, accelerate Aβ_{42} clearance, scavenge ROS, Reduce hyperphosphorylated tau, and alleviate glial cell activation	*In vivo*/*In vitro*	Zhang et al., 2024[201]
	Silica nanobowls	NB	Lipid (DOPE), (p-NIPAM, poly(N-isopropylacrylamide))	150	Aβ	Scavenge amyloid oligomers from neuron	*In vitro*	Sant et al., 2021[202]
	Chiral mesoporous silica nanospheres	*l*-mSiO_2	Micelles with chiral and NH_2 groups	∼90	Aβ	Reduce Aβ_{42} aggregation, alleviate Aβ_{42}-induced cytotoxicity on neuronal SH-SY5Y cells	*In vitro*	Xu et al., 2023[203]

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Table 1. continued

Types		Name	Modification/Loading	Size (nm)	Targeted Pathogenesis	Molecular mechanisms and Therapeutic Efficacy	*In vivo*/*In vitro*	ref
	Magnetic mesoporous silica NPs	THN	PEG-CeO_2 NPs (CNPs), antitau antibody (AT8), iron oxide NPs	~78.5	Tau	Specifically activate the autophagy pathway, promote the degradation of tau	*In vivo*/*In vitro*	Sun et al., 2021[189]
	Graphene oxide	l-GO; s-GO	/	0.5−3 μm; <15 nm	Aβ	Inhibit Aβ peptide monomer fibrillation, clear mature amyloid fibrils, and mitigate the cytotoxicity of Aβ peptide amyloids	*In vitro*	Yang et al., 2015[125]
	Graphene oxide	GO	/	40−60	Aβ	Activated autophagy of both microglia and neurons through the AMPK/mTOR pathway to promote Aβ clearance and protect neurons	*In vitro*	Li et al., 2020[204]
Carbon-based NPs (CNPs)	Fullerene	f-Gd@C_{82}	Hydrogen-binding sites and charged groups	4.8 ± 0.9	Aβ	Relieve neuronal cytotoxicity via inhibition of Aβ aggregation	*In vitro*	Yin et al., 2024[21]
	Nitrogen-doped CNPs	C_3N nanodots	/	4.5 ± 0.4	Aβ	Reduce the Aβ aggregation, restore synaptic loss in AD mice	*In vitro*/*in vivo*	Yin et al., 2023[22]
	Congo red-derived carbon dots	CRCD	/	2.7−3.9	Aβ, tau	Inhibit tau and Aβ aggregation, and effectively penetrates the BBB in the zebrafish model	*In vitro*/*in vivo*	Zhang et al., 2024[205]
	Selenium QDs	SeQDs	Rhodamine modified	5.0	Aβ, oxidative stress, neuroinflammation	Inhibit Aβ aggregation, reduce inflammatory reaction, mitochondrial dysfunctions and oxidative stress, and improve cognitive function in AD mice	*In vitro*/*in vivo*	Guo et al., 2021[102]
Quantum dots (QDs)	MoS_2 QDs	MoS_2 QDs/macrophage membrane (MM)	Macrophage membrane-modified	125.62 ± 4.132	Aβ, oxidative stress	Target the brain, scavenge ROS and resist Aβ deposition, reduce Aβ-mediated cytotoxicity, and improve the exploration desire and learning ability of APP/PS1 mice	*In vitro*/*in vivo*	Qi et al., 2024[206]
	Carbon QDs (CQDs)	Cur-CQDs	Cross-linked with curcumin	6.9 ± 1.1	Aβ, tau	Modulates Aβ aggregation and tau hyperphosphorylation	/	Lim et al., 2024[103]
	Chitosan	CHG NPs	Cross-linked with glutaraldehyde	~100	Aβ	Image Aβ plaques and inhibit Aβ deposition	*In vitro*/*in vivo*	Wang et al., 2021[180]
	Chitosan	GH-loaded chitosan	Galantamine hydrobromide loaded	~286	AChE	Allowed the prolonged release of the incorporated drug	*In vitro*	Georgieva et al., 2023[179]
	PLGA	BBR/PLGA-Tet NPs	berberine-loaded, Tet-1 peptide conjugate	264.2 ± 44.7	Oxidative stress, neuroinflammation, synapse dysfunction, Tau, and Aβ	reduce neuronal oxidative stress, Aβ plaques, and NFT accumulation and enhance hippocampal synaptic function	*In vitro*/*in vivo*	Saleh et al., 2024[178]
Polymeric NPs (PNPs)	Dendrimers	APBP	Ab peptide, p-Nrf2	21	Oxidative stress, neuroinflammation	Reduce ROS level, decrease Aβ burden, alleviate glial cell activation, and eventually enhance cognitive functions in APPswe/PSEN 1dE9 model mice	*In vitro*/*in vivo*	Liu et al., 2021[182]
	Nanogels	AOC NGs	Oxytocin (OT)-loaded angio-pep-2-modified	122.0	Neuroinflammation	Inhibit microglial activation and reduce inflammatory cytokine levels	*In vitro*/*in vivo*	Ye et al., 2022[106]
	Micelles	TT-NM/Rapa	Fusion peptide TPL modified, rapamycin-loaded	41.05 ± 1.20	Aβ, tau	Reduce neurotoxic Aβ and p-tau, and ameliorate memory defects	*In vitro*/*in vivo*	Xu et al., 2022[181]

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Table 1. continued

Types		Name	Modification/Loading	Size (nm)	Targeted Pathogenesis	Molecular mechanisms and Therapeutic Efficacy	*In vivo*/*In vitro*	ref
Lipid-based NPs (LNPs)	Liposomes	RVGMAN, PenMAN	Glucose transporter-1 (glut-1) targeting ligand mannose (MAN) and cell-penetrating peptide (CPP)	167.8 ± 2.47, 172.0 ± 3.09	Aβ	Delivery the ApoE2 gene to brain cells, resulting in higher transfection efficiency	*In vitro*/*in vivo*	Arora et al., 2021[207]
	Liposomes	DPMT@PEI/*miR-195*	Dual modification with MAN and TAT peptides	<200	Aβ, tau	Mitigates Aβ production and tau protein hyperphosphorylation by downregulating APP and BACE1 protein expression and discourages M1 microglial polarization	*In vitro*/*in vivo*	Su et al., 2024[163]
	Niosomes	RIV + NAC niosomes	Rivastigmine/N-acetyl cysteine	162.4	AChE	Sustained drug release up to 2 days, enhanced combinatory effects, direct nose-to-brain drug delivery	*In vitro*/*in vivo*	Kulkarni et al., 2021[170]
	Transfersomes	DPZ-HA-TFS	Hyaluronic acid-coated and loaded with donepezil hydrochlorid	227.5	AChE	Intranasal DPZ-HA-TFS elicited superior brain bioavailability than intravenous or oral DPZ	*In vitro*/*in vivo*	F. Salem et al., 2024[165]
	Ethosomes	DH-loaded ethosomal gel	Loaded with donepezil hydrochlorid	110.06 ± 1.91	AChE	The *in vitro* and *ex vivo* drug permeation almost 100% after a period of 24 h	*In vitro*	Gangopadhyay et al., 2023[166]
	Solid lipid NPs	M + T SLNs	Load with memantine hydrochloride and tramiprosate	159.9 ± 0.569	Aβ	Enhance neuroprotective effects, improve pharmacokinetic profile, enhance spatial memory performance, decrease Aβ plaques in rat hippocampus	*In vitro*/*in vivo*	Shivananjegowda et al., 2023[167]
	Nanostructured lipid	DPL/AST-NLCs	Co-loaded with donepezil and astaxanthin	149.9 ± 3.21	Aβ, oxidative stress, inflammation, AChE	significantly higher antiamyloidogenic, antioxidant, antiacetylcholinesterase, anti-inflammatory, and antiapoptotic effects, resulting in significant improvement in the cortical and hippocampal histopathology	*In vitro*/*in vivo*	Shehata et al., 2023[208]
Metal−organic frameworks (MOFs)	Porphyrinic MOFs	Zr-MOF, Al-MOF, Ni-MOF, Hf-MOF	Modified with Aβ-targeting peptide LPFFD	90−700	Aβ	Inhibit Aβ aggregation, attenuate Aβ-induced toxicity and extend the life span of the AD transgenic C. elegans CL2006 strain	*In vitro*/*in vivo*	Yu et al., 2019[194]
	Ceria-decorated MOF	CeNPs/RA@MIL-100/siSOX9 (CeRMS)	Loaded with small interfering RNA (siSOX9) and retinoic acid (RA)	100−200	Oxidative stress	Alleviating oxidative stress, reducing neuronal apoptosis, increasing neurite length, and improving cognitive function in aged 3 × Tg-AD mice	*In vitro*/*in vivo*	Yu et al., 2020[209]
	Ce/Zr MOF	Ce/Zr-MOF@Cur-Lf	Loaded with curcumin, coated with hyaluronic acid and lactorferrin	286.0 ± 2.77	Oxidative stress	Reduce ROS levels, clear Aβ plaques, modulate microglia and astrocyte activity, decrease inflammatory factors, and inhibit AchE	*In vitro*/*in vivo*	Yang et al., 2024[108]
	Zn-CA MOF	TR/ZC/RNAi/AAP (TR-ZRA)	Modified with transferrin receptor aptamers and loaded with CD22shRNA plasmid and Aβ aptamer	93.3	Immune environment	Promote neuronal activity and decrease inflammation level, enhance learning, and memory abilities in AD mice	*In vitro*/*in vivo*	Su et al., 2023[195]

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to AuNPs, CeO_2 NPs are noteworthy for their strong and recyclable ROS scavenging properties, enabled by their reversible Ce^{3+}/Ce^{4+} redox cycle.[116] Kwon et al. reported that triphenylphosphonium-conjugated ceria (TPP-ceria) NPs alleviated reactive gliosis and mitochondrial damage in a 5XFAD transgenic AD mouse model, highlighting the potential of ceria NPs in mitigating oxidative stress and neuroinflammation.[117]

The integration of photocatalysis and multitarget synergism further expands the scope of MNPs in AD treatment. For instance, Ge et al. synthesized KLVFF@Au-CeO_2 (K-CAC) nanocomposites by functionalizing the central surface of Au nanorods (Au NRs) with the Aβ-targeted inhibitory peptide KLVFF and coating both ends with CeO_2.[118] This design leverages the combined antioxidant properties of CeO_2 and the photothermal effects of Au NRs to degrade Aβ polymers, inhibit monomer aggregation, and alleviate oxidative stress, presenting a novel therapeutic strategy for AD. Similarly, Park et al. developed multifunctional MnO_2 nanoparticles (MnO_2 NPs) functionalized with an anti-Aβ antibody and coated with a BBB-penetrating terpolymer (Ab-TP-MDNPs). These NPs efficiently cross the BBB, target Aβ plaques, scavenge ROS, and generate oxygen, alleviating hypoxia and oxidative stress. This cascade of effects further reduces neuroinflammation, improves vascular function, enhances cerebral blood flow, and normalizes lymphatic Aβ clearance, demonstrating a comprehensive strategy for AD intervention.[119]

Despite their potential, clinical translations of these metallic nanomaterials face limitations, including safety concerns, scalability issues, and an incomplete understanding of their long-term effects on biological systems. Rigorous preclinical evaluations and interdisciplinary collaborations will be essential to address these gaps and facilitate the integration of metallic nanomaterials into therapeutic protocols. Looking ahead, the continued exploration of hybrid systems combining metallic nanomaterials with other nanoplatforms such as polymeric or lipid-based carriers may provide synergistic benefits. These integrated approaches could amplify therapeutic efficacy, enhance delivery precision, and reduce adverse effects, paving the way for more effective and sustainable treatment strategies.

3.2. Carbon-Based Nanoparticles (CNPs)

CNPs, such as fullerenes, carbon nanotubes (CNTs), and graphene, have been widely investigated for various biomedical applications owing to their peculiar structure and features. Graphene, in particular, offers advantages in drug delivery and biosensing due to its high electrical conductivity and ease of surface modification.[120−123] CNTs are widely recognized in biosensing applications due to their high specific surface area.[124] These materials' nanoscale size, high surface area, and ability to cross the BBB make them highly desirable in addressing the complex challenges of AD.

Early pristine CNPs, such as unmodified C_{60}, graphene, and CNTs, were initially explored for their ability to inhibit Aβ aggregates and reduce the level of oxidative stress. For example, graphene and graphene-oxide (GO) nanosheets, owing to their high hydrophobicity, can disrupt peptide side chains to form a highly ordered hydrophobic core during the Aβ aggregation process.[125,126] Additionally, they can insert into mature Aβ fibrils and extract peptides destructively. Similarly, CNTs can interact with Aβ through hydrophobic interactions and π-π stacking, effectively inhibiting fibrillation.[127−129] Despite these desired effects, pristine forms often faced challenges, such as limited solubility, potential cytotoxicity, and insufficient specificity for targeting disease-specific proteins or pathways. Studies have shown that the use of pristine CNTs can trigger inflammatory responses and reduce cell viability. Additionally, the aggregation of CNTs via van der Waals interactions has been found to adversely affect cellular responses and induce pulmonary toxicity *in vivo*.[130,131] Similarly, the hydrophobic nature of GO nanosheets leads to poor water dispersibility, which can result in acute cell membrane toxicity and other biotoxicity.[132,133]

Chemical modification or doping can effectively mitigate the aforementioned limitations, thereby significantly broadening the potential applications of CNPs. For example, functionalized single-walled carbon nanotubes (SWCNTs) restored normal autophagy by reversing abnormal activation of mTOR signaling and deficits in lysosomal proteolysis, thereby facilitating the elimination of autophagic substrates.[134] In addition, current research has shown that modifications of C_{60}, including hydroxylation, pentoxifylline conjugation, PEGylation, and metal embedding (e.g., f-Gd@C_{82}),[21,135,136] can improve their water solubility, while still maintaining their efficacy in inhibiting Aβ fibrillogenesis and scavenging free radicals. Cellular assays additionally demonstrate that these modified compounds confer protection to neural cells against oxidative damage induced by Aβ and ROS.

Graphitic carbon nitride (g-C_3N_4), the most stable carbon nitride allotrope, has attracted significant interest for its outstanding properties,[137−141] particularly its surface functionalities ($-NH_2/-NH-/=N-$), which can serve as effective ligands for metal ion adsorption through chelation or redox reactions.[142,143] Researchers have developed g-C_3N_4-based nanomaterials, such as platinum(II)-coordinated g-C_3N_4 nanosheets (g-C_3N_4@Pt), which inhibit Aβ aggregation[144] and reduce oxidative stress.[145] These nanosheets also act as nanochelators, disrupting Aβ-Cu^{2+} aggregates and shielding cells from Aβ-induced toxicity. Under light irradiation, g-C_3N_4 nanosheets further demonstrate effective inhibition of Aβ aggregation and toxicity.[146] In contrast to traditional metal chelators, these nanosheets can cross the BBB, which overcomes the drawbacks of unstable small chemicals or peptides and thereafter can be actively transported out of the brain. C_3N, another nitrogen-doped CNP, has also shown promise in AD treatment. C_3N nanodots, which are ultrasmall in size, have been reported to alleviate aggregation-induced neuron cytotoxicity, rescue neuronal death, and prevent neurite damage *in vitro*.[22] Importantly, they reduce the global cerebral Aβ levels, particularly in fibrillar amyloid plaques, and restore synaptic loss in AD mice. Consequently, these C_3N nanodots significantly ameliorate behavioral deficits in APP/PS1 double transgenic male AD mice. Moreover, analyses of critical tissues display no obvious pathological damage, suggesting that C_3N nanodots are biologically safe. The integration of heterojunction nanomaterials combined with superior properties heralds a new tendency in therapeutic studies and treatments for AD.

3.3. Quantum Dots (QDs)

Quantum dots (QDs), with diameters ranging from 2 to 10 nm, exhibit unique fluorescence properties due to quantum confinement effects, enabling size-dependent photoluminescence across the ultraviolet-to-infrared spectrum. Their strong, stable luminescence, coupled with the ability to conjugate with biomolecules, makes QDs a promising platform for both

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diagnostic and therapeutic applications in diseases such as AD and cancer.[147] QDs are broadly categorized into two types based on their composition: inorganic semiconductor QDs and organic carbon-based QDs. Traditional inorganic QDs, typically derived from II−VI semiconductor materials (e.g., CdS, ZnS, CdSe, ZnSe, and CdTe), offer excellent optical properties but face limitations due to cytotoxicity from metal ion leaching (e.g., Cd^{2+}), restricting their use in AD treatment. To mitigate this toxicity, core−shell structures (e.g., ZnS) and biocompatible surface modifications (e.g., poly(ethylene glycol) [PEG], *N*-acetyl-L-cysteine [NAC], and dihydrolipoic acid [DHLA]) have been explored. These strategies enhance QD stability and enable their application in amyloid and tau protein detection, as well as Aβ fibril inhibition.[148−150] For instance, Chen et al. developed dopamine-modified $CuInS_2$/ZnS core−shell QDs with high luminescence and low toxicity for tau protein detection.[151] Similarly, Xiao et al. utilized NAC-coated QDs (NAC-QDs) to impede $A\beta_{40}$ fibrillization, identifying hydrogen bonding interactions as the key mechanism of inhibition.[149] Despite these advancements, concerns over inorganic QDs have driven research toward carbon-based QDs, which offer superior biocompatibility for biomedical applications.

Carbon dots (CDs), alternatively referred to as carbon quantum dots (CQDs), have gained substantial attention across various fields, including fluorescence detection and disease treatment, thanks to their small size and exceptional biocompatibility.[152−154] These NPs consist of a core composed of sp^2/sp^3 hybridized carbon atoms with surface functionalization by oxygen- and nitrogen-containing groups. The synthesis of CQDs can be achieved through straightforward, solvent-free methodologies, including pyrolysis, hydrothermal treatment, and microwave-assisted techniques, utilizing a diverse array of cost-effective organic precursors.[155] These characteristics endow CQDs with numerous advantages, such as cost-effectiveness, straightforward synthesis, exceptional biocompatibility, photoluminescent properties, scalability, and controllable quality.[156−158] Chung et al. utilized branched polyethylene imine (bPEI) to passivate CQDs, establishing a straightforward method to suppress Aβ peptide self-assembly and mitigate Aβ-induced neurotoxicity by employing visible light-active and biocompatible bPEI@CQDs as β-sheet breakers.[159] Ravit Malishev et al. synthesized enantiomeric CQDs utilizing chiral lysine, specifically L-lysine and D-lysine, which yielded L-Lys CQDs and D-Lys CQDs, respectively.[160] Their findings indicated that L-Lys CQDs effectively inhibited the self-aggregation of $A\beta_{42}$ and mitigated its cytotoxic effects. The authors hypothesized that the positively charged amino groups ($-NH_3^+$) present on the surface of L-Lys CQDs disrupted the electrostatic interactions of the Aβ peptides. Yan et al. successfully synthesized epigallocatechin gallate (EGCG)-loaded glucose-derived carbon quantum dots (gCQDs-E) utilizing glucose as the precursor molecule.[161] The gCQDs-E demonstrated efficacy in mitigating the cytotoxicity linked to amyloid aggregation and facilitated the clearance of Aβ peptide deposits across the BBB in APP/PS1 transgenic AD model mice. This intervention concurrently ameliorated memory deficits, indicating its potential as a therapeutic strategy for AD. Additionally, polyphenol nanoparticles have shown similar effects.[162] Lim et al. successfully synthesized curcumin carbon quantum dots (Cur-CQD) utilizing curcumin as a precursor.[103] *In vitro* cellular assays demonstrated that Cur-CQD effectively mitigated the aggregation of Aβ peptides and the hyperphosphorylation of tau proteins. These results underscore the potential of employing various precursor molecules, morphologies, and structures of carbon dots to impart distinct anti-AD target functionalities.

3.4. Lipid-Based Nanoparticles (LNPs)

LNPs, composed of organic lipid molecules such as fats, oils, and related compounds, have emerged as promising nanocarriers due to their biocompatibility, biodegradability, and proficiency in encapsulating therapeutic agents. Various LNP systems—including liposomes,[163] niosomes,[164] transfersomes,[165] ethosomes,[166] solid lipid nanoparticles (SLNs),[167] and nanostructured lipid carriers (NLCs)—have also been extensively studied for AD treatment. These carriers enhance drug stability, prevent premature degradation, and facilitate targeted delivery, making them attractive multifunctional platforms.[168,169]

Several studies have explored liposome-loaded drug transport systems as a potential strategy for AD treatment. The choice of drugs, liposome composition, and surface modifications are critical factors in optimizing the effectiveness of these delivery systems. For example, Su et al. developed nanoliposomes functionalized with P-aminophenyl-α-D-mannopyranoside (MAN) and the cationic cell-penetrating peptide TAT to enhance BBB penetration.[163] These DPMT@PEI/miR-195 liposomes significantly reduced Aβ plaques, tau hyperphosphorylation, and microglial polarization in an AD mouse model, demonstrating the potential for both early and advanced disease stages.

In addition to liposomes, niosomes—vesicular structures formed by combining cholesterol with alkyl or dialkyl polyglycerol ether-derived nonionic surfactants—have been proposed as liposome alternatives for drug delivery.[164] The lipid component of niosomes provides physical shape and structural support, while the nonionic surfactant constitutes the primary structural component. This nonionic surfactant has a hydrophilic head and a hydrophobic tail, making it effective for carrying drug molecules. For instance, a novel dual drug-loaded niosomes system for nasal delivery of rivastigmine and N-acetyl cysteine has demonstrated excellent drug entrapment efficiency, stability, sustained release, and direct nose-to-brain delivery.[170]

Transfersome, another class of lipid-based vesicles, typically contains four different components: phospholipids, an edge activator, a low concentration of ethanol, and water.[171] The phospholipids form a bilayer, while the edge activator stabilizes the bilayer and allows the vesicle to deform by creating a high radius of curvature.[172] Due to their high flexibility and elasticity, transfersomes offer a better advantage over liposomes and niosomes. Additionally, their high drug-loading capability and deeper penetration make them a promising drug carrier for treating AD.[165]

Ethosomes are nanoscale carriers composed of phospholipids, ethanol, and water, known for their ability to penetrate the skin. Gangopadhyay et al. prepared an ethosomal intranasal gel loaded with donepezil hydrochloride to enhance drug transport across the BBB, thereby reducing plasma concentrations and minimizing oral drug-related side effects. The results demonstrated that the optimized gel formulation achieved nearly 100% drug permeation after 24 h, both *in vitro* and *in vivo*.[166]

Despite the promising outcomes observed in preclinical studies, the clinical application of LNPs for AD therapy

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remains in its early stages. For successful translation into clinical practice, several key issues must be addressed, including the evaluation of safety profiles, long-term benefits, and verification of therapeutic efficacy through comprehensive assessments. Furthermore, the production cost of LNPs, particularly those designed for targeted delivery, is high, which poses a significant barrier to their widespread use.[173,174] To overcome these challenges, further research is required to enhance the targeting efficiency and specificity of these NPs, as well as to develop lipid formulations that improve the stability of drugs, especially those prone to rapid degradation in biological environments. Additionally, LNP drug delivery systems can be integrated with gene therapy or RNA-based treatments and serve as nanoscale carriers for imaging agents or diagnostic markers,[175] facilitating early disease detection and monitoring of disease progression.

3.5. Polymeric Nanoparticles (PNPs)

PNPs are solid particles composed of organic colloids with natural, synthetic, or hybrid polymeric materials. These NPs, ranging in size from 10 to 1,000 nm, can be engineered from various monomers using diverse polymerization techniques, allowing customization for specific biomedical applications.[176] They are highly versatile and particularly valuable for brain-targeted therapies,[177] offering improved biodegradability, biocompatibility, stability during storage, and extended shelf life. These properties enable the controlled and sustained release of therapeutic agents, enhancing their potential for effective treatment delivery.

PLGA is one of the most widely studied polymers due to its controlled and sustained-release properties, low toxicity, and biocompatibility with cells and tissues. PLGA has been approved by both the FDA and the European Medicine Agency for applications in vaccines, drug delivery, and tissue engineering. To facilitate the BBB entry, Saleh et al. used PLGA to synthesize a brain-targeted formulation: berberine-loaded poly(lactic-*co*-glycolic acid)/Tet-1 peptide NPs (BBR/PLGA-Tet NPs).[178] This formulation reduces neuronal oxidative stress, Aβ plaques, and NFT accumulation and enhances hippocampal synaptic function. Chitosan is a cationic linear polysaccharide that is also biodegradable and biocompatible. Chitosan NPs have unique features, such as mucoadhesive properties and intrinsic bioactivity, which not only promote drug penetration into the brain via intranasal administration[179] but also represent anti-AD therapeutics themselves.[180]

Nanogels are submicrometer-scale hydrogels formed by the physical or chemical cross-linking of polymers. They can combine the hydration and multifunctionality of hydrogels with the benefits of nanocarriers for early AD treatment.[106] Comprised of amphiphilic polymers, micelles are distinguished by their distinctive spherical morphology, attributable to the segregation of hydrophobic sectors from hydrophilic counterparts. Micellar drug delivery systems are popular due to their small size, long circulation time, good stability, and targeting. Xu et al. designed a ROS-responsive targeted micelle (TT-NM/Rapa) to precisely deliver rapamycin to neurons in AD lesions and achieve efficient release in response to elevated intracellular levels of ROS, which greatly strengthened the regulation of rapamycin on autophagic flux for AD therapy.[181] Dendrimers are highly branched spherical polymers with a unique 3D structure consisting of an inner core and multiple hyperbranches, each with functional groups at the end. Their size is typically 10 to 100 nm, depending on the number of hyperbranches. This branched structure allows for the attachment of bioactive molecules, thus enhancing their potential for targeted drug delivery. In addition, the peripheral groups facilitate BBB penetration, making dendrimers promising therapeutics for AD.[182]

PNPs are at the forefront of drug delivery innovation, offering numerous advantages that are particularly relevant for addressing AD. However, most of these systems are still in the animal testing phase, where the interaction between the polymer and drug complicates the drug's metabolism kinetics *in vivo*. For instance, compared to traditional drugs, factors such as the polymer-to-drug ratio, molecular weight, degree of crystallinity, particle size, and even the preparation process all influence drug release in a bioendogenous environment. The metabolic pathways of polymeric drugs in the body remain unclear. Moreover, the use of synthetic polymers can be limited by factors such as cost, purity, and undesirable toxicity profiles.

3.6. Silica Nanoparticles (SiO_2 NPs)

Silica nanoparticles (SiO_2 NPs), especially MSNs, have gained attention for biomedical applications due to their superior physicochemical and biological properties.[183−185] A key advantage of MSNs is their extensive surface area, resulting from their porous structure, which offers efficient drug loading and controlled release capabilities, making them ideal drug delivery systems in AD treatment. Surface-modified MSNs take these advantages a step further, allowing for targeted drug delivery to specific regions in the brain affected by AD and controlled release to minimize side effects. Consequently, the design of MSNs and their multifunctional derivatives for drug delivery has become a major focus in AD treatment.[186]

For instance, Wang et al. developed a multifunctional MSN-based nanocarrier, CICe@M-K, by fixing peptide K (CKLVFFAED) and ultrasmall CeO_2 NPs onto the surface of MSNs and encapsulating curcumin (Cur) and photosensitizer (IR780) in its pores, thereby achieving synergistic AD treatment.[187] Specifically, both Cur, released by NIR irradiation, and peptide K can bind to Aβ through multiple interactions, including $\pi-\pi$ stacking, hydrophobic interaction, and hydrogen bonding, thereby inhibiting Aβ aggregation. In addition, CeO_2 NPs on the MSN surface synergize with Cur to eliminate ROS, and the short peptide K enhances its ability to cross the BBB and target Aβ. *In vivo* assays show that the proposed CICe@M-K nanocarrier can improve memory deficits in APP/PS1 AD mice.

To achieve the potential of controlled and targeted delivery of drugs to improve *in vivo* performance in AD treatment, Singh et al. developed brain-targeted lipid-coated MSNs (MCM-41) loaded with berberine (BB), MSNs-BB-L.[188] This nanocarrier demonstrated AChE inhibitory activity significantly higher than those of MCM-41 and pure BB solutions. The study also confirmed that MSNs-BBR-L effectively inhibited Aβ fibrillation and reduced the level of malondialdehyde levels. *In vivo*, both pure BB and MSNs-BBR-L treatments resulted in a significant reduction in BACE-1 levels in AD animals compared to scopolamine-intoxicated mice. These findings underscore the therapeutic potential of MSNs-BB-L for AD treatment.

Autophagy-activating strategies have shown therapeutic potential for AD in various studies; however, their further development is hindered by low efficacy and significant side

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effects, primarily due to a lack of selectivity for diseased cells. Sun et al. reported a rationally designed MSN-based tauopathy-homing nanoassembly (THN) for the autophagy-mediated selective clearance of pathogenic tau in AD.[189] THN is composed of active ingredients including CeO_2 NPs, antitau antibody (AT8), and magnetic MSN. THN can bind to hyperphosphorylated and/or aggregated tau and selectively accumulate in cells undergoing tauopathy. The THN further promotes the clearance of pathogenic tau accumulation by stimulating autophagic flux, thereby rescuing neuronal viability and cognitive functions in AD rats. This study presents a promising nanotechnology-based strategy for tauopathy-homing and autophagy-mediated specific removal of pathogenic tau in AD.

While MSNs offer significant advantages as nanocarriers in drug delivery systems, challenges remain,[186] including difficulty in preparing MSNs with uniform size and shape, reduced drug encapsulation efficiency, compatibility issues, poor degradability, potential cargo leakage, variability in cell uptake, off-target effects, immune recognition, and scalability concerns. Addressing these limitations is essential for fully harnessing the potential of MSNs in developing innovative and effective therapeutic strategies.

3.7. Metal−Organic Frameworks (MOFs)

MOFs are crystalline materials formed by coordinating metal ions or clusters with organic ligands.[190] Due to their high porosity, suitable size, large specific surface area, tunable structure, easy functionalization, and chemical stability, MOFs have attracted extensive attention as promising candidates for various applications, from the chemical industry to biomedicine.[191,192] Several approaches have been proposed for utilizing MOFs in AD management, including exploiting the inherent metal and ligand properties of MOFs to direct scavenging of Aβ and reduction of Aβ mediated neurotoxicity[107,193,194] or serving as multifunctional drug delivery vehicles.[108,195,196]

For instance, Mensinger et al. evaluated the adsorption properties of seven different MOFs for the Aβ peptide.[107] The results demonstrated that UiO-66, MIL-88B, and MIL-53 can not only strongly adsorb the Aβ peptide but also retain it almost completely. Yu et al. synthesized four classical kinds of porphyrin MOF (PMOF) NPs (Zr-MOF, Al-MOF, Ni-MOF, Hf-MOF) as a Cu^{2+} chelator and photooxidant to inhibit Aβ aggregation.[194] It was found that Hf-MOF was the most efficient Aβ photooxidant. The Hf-MOFs modified with an Aβ-targeting peptide can not only enhance Hf-MOFs targeting cellular Aβ to decrease Aβ-induced cytotoxicity but also improve Aβ photooxidation. The results obtained from *in vivo* experiments verified that modified Hf-MOFs could decrease Aβ-induced toxicity and extend the longevity of the commonly used transgenic AD model *Caenorhabditis* elegans CL2006.

Yang et al. recently introduced the multifunctional NP, Ce/Zr-MOF@Cur-Lf, which utilizes Ce/Zr-MOF as a carrier, loaded with curcumin, and surface-modified with lactoferrin (Lf).[108] Ce/Zr-MOF exhibits antioxidant properties,; curcumin possesses anti-inflammatory and Aβ-lowering effects, while Lf specifically targets the brain. Studies have demonstrated that Ce/Zr-MOF@Cur-Lf can effectively cross the BBB and enter the brain and improve various pathological features in AD model mice, such as neuronal damage, Aβ deposition, cholinergic system dysfunction, oxidative stress, and neuroinflammation through a multitarget mechanism. Similarly, Su et al. constructed a Zn-CA MOF-based nanodrug system (TR-ZRA), camouflaged by an autologous erythrocyte membrane and targeted to penetrate the BBB under the action of transferrin receptor aptamer.[195] The system is loaded with CD22 shRNA plasmids to silence the abnormally high levels of expression of CD22 molecules in aged microglia. TR-ZRA can also enhance the ability of microglia to phagocytose Aβ and reduce complement activation, thereby promoting neuronal activity and reducing inflammation levels in AD brains. In addition, TR-ZRA is also loaded with Aβ aptamers, which can be used for rapid and low-cost monitoring of Aβ plaques *in vitro*. Studies have shown that TR-ZRA can significantly improve the learning and memory abilities of AD mice. The study provides a promising strategy and a new immunotherapy target for treating AD.

The unique properties of MOF-based NPs have opened new avenues for nanodrug and delivery systems; however, challenges persist. The biological safety of MOFs is the most pressing issue that needs to be addressed in clinical research. Given the rich diversity of the structure and types of MOFs, along with the complexity of the biological environment, accurately assessing the toxicity and biocompatibility of MOFs is a long-term and challenging task. Moreover, the impact of shape, size, surface chemistry, and composition of MOF nanomaterials on theranostic applications must be further optimized during synthesis to better meet the needs of personalized treatments.

4. CONCLUSION AND PERSPECTIVES

Despite the significant progress in preclinical research using various nanomedicines for AD treatment, none has achieved successful clinical translation yet. Several critical challenges must be addressed to advance this promising field, particularly in the rational design of nanomedicines, the optimization of manufacturing processes, and the assurance of biological safety. First, most research focused on documenting macroscopic biological effects, with limited investigation of the molecular mechanisms. This knowledge gap hinders a comprehensive understanding of the structure−activity relationships between nanodrugs and their anti-AD effects, limiting the rational design and optimization of nanomedicines. Second, reproducibility and scalability in the synthesis of nanomaterials remain significant obstacles. Variations in size, shape, surface properties, and functionalization can affect therapeutic efficacy and safety, complicating regulatory approval and clinical translation. Another critical challenge is the potential toxicity of the nanomaterials. These materials may induce unpredictable effects on cellular physiology or accumulate in various organs, resulting in adverse outcomes.[210−213] For instance, certain NPs might in fact facilitate Aβ fibrillation, contribute to bioaccumulation-induced neurotoxicity,[214] disrupt critical organelles such as mitochondria, lysosomes, and the endoplasmic reticulum in macrophages, and trigger excessive ROS production along with pro-inflammatory responses[215] (with many in favor of the AD progression on the contrary). Thus, addressing these issues is crucial to ensuring consistent, functional, and clinically viable nanomedicine formulations.

Despite these challenges, developing multitargeting and multifunctional NPs offers a promising path forward.[216] These advanced designs have the potential to address the multifactorial nature of AD by simultaneously targeting key mechanisms, such as Aβ aggregation, tau protein stabilization, and neuroinflammation. Such approaches could improve therapeutic efficacy, minimize adverse effects, and enhance

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the overall utility of nanomaterial-based drug delivery systems. Further opportunities for innovation arise from ongoing research into new biomarkers for AD.[217] For instance, the recognition of vascular dysfunction as a significant contributor to AD pathology highlights a novel and promising therapeutic target.[218] Exploring these emerging pathways has the potential to enhance current strategies and expand the range of nanomedicine applications. The successful translation of these advancements into clinical practice necessitates close collaboration among materials scientists, neuroscientists, and clinicians to bridge the gap between preclinical research and practical application. Such collaborative efforts are critical for overcoming existing barriers and fully unlocking the potential of nanomedicine to transform AD treatment.

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