RESEARCH PAPER

Blood-Brain Barrier-Targeted Nanocarriers for Alzheimer's Disease: Molecular Mechanisms, Therapeutic Advances, Clinical Translation and Future Perspectives

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Abstract

Alzheimer's disease (AD) is the most common neurodegenerative disorder and a major cause of dementia worldwide. The disease is characterized by amyloid-β plaque deposition, tau hyperphosphorylation, neuroinflammation, oxidative stress, and progressive neuronal loss. However, effective treatment remains challenging due to the blood–brain barrier (BBB), which restricts the delivery of most therapeutic agents to the brain.Nanocarrier-based drug delivery systems have emerged as promising approaches for overcoming BBB-associated limitations. Various nanocarriers, including liposomes, polymeric nanoparticles, solid lipid nanoparticles, dendrimers, exosomes, and inorganic nanoparticles, can improve BBB penetration, enhance drug bioavailability, provide controlled release, and reduce systemic toxicity. Surface functionalization with targeting ligands further facilitates brain-specific drug delivery through receptor-mediated transport pathways..This review highlights the molecular mechanisms of AD, BBB structure and transport pathways, and recent advances in BBB-targeted nanocarriers. Current challenges, clinical translation prospects, and future opportunities for nanomedicine-based AD therapy are also discussed. BBB-targeted nanocarriers offer significant potential for improving therapeutic efficacy and developing effective disease-modifying treatments for Alzheimer's disease.

Keywords: Alzheimer's disease; Blood–brain barrier; Nanocarriers; Brain targeting; Neurodegeneration; Nanomedicine.

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Introduction

Alzheimer's disease (AD) is the leading cause of dementia and one of the most challenging disorders in modern medicine. The disease evolves gradually over years or decades and is clinically characterized by memory impairment, executive dysfunction, language difficulty, behavioural disturbance, and progressive loss of independence. Pathologically, AD is associated with extracellular amyloid-beta (Aβ) plaques, intracellular neurofibrillary tangles composed of hyperphosphorylated tau, synaptic loss, neuroinflammation, oxidative stress, cerebrovascular dysfunction, and neuronal death. The worldwide burden of dementia continues to rise with ageing populations, and global agencies estimate that tens of millions of people are currently affected, with numbers projected to increase substantially by 2050.

The currently available therapeutic landscape remains limited. Cholinesterase inhibitors such as donepezil, rivastigmine, and galantamine improve cholinergic neurotransmission and may temporarily improve symptoms in mild-to-moderate disease. Memantine, an N-methyl-D-aspartate receptor antagonist, is used in moderate-to-severe AD to modulate excitotoxicity. More recently, monoclonal antibodies targeting aggregated Aβ have provided evidence that amyloid removal can influence disease biomarkers and clinical decline in selected patients. Nevertheless, these approaches are constrained by modest efficacy, safety concerns, high cost, infusion requirements, and patient selection issues. Many disease-modifying agents also fail because they do not reach adequate concentrations in the brain.

The blood-brain barrier (BBB) is a central obstacle in AD therapy. It is a dynamic interface between the blood and central nervous system that maintains ionic balance, regulates nutrient entry and protects the brain from xenobiotics. However, the same features that protect the brain also restrict drug delivery. Tight junctions limit paracellular transport, efflux pumps remove many xenobiotics, and enzymatic barriers degrade susceptible drugs. As a result, most therapeutic molecules, particularly peptides, proteins, antibodies, nucleic acids and hydrophilic compounds, show poor BBB penetration.

Nanomedicine provides a rational strategy to address this challenge. Nanocarriers can improve solubility, protect

drugs against enzymatic degradation, extend circulation time, reduce peripheral toxicity, promote controlled release and enable surface functionalization with ligands that interact with BBB transport systems. Furthermore, nanocarriers may co-deliver multiple therapeutics, allowing simultaneous modulation of Aβ, tau, oxidative stress and neuroinflammation. Such multi-targeted strategies are particularly attractive because AD is not driven by a single pathway.

Despite major progress, the translation of BBB-targeted nanocarriers remains difficult. A formulation that crosses an in vitro BBB model may not show meaningful brain exposure in vivo. Animal models often fail to reproduce the complexity of human AD, and nanoparticle behaviour is influenced by disease stage, ageing, protein corona formation and immune clearance. Therefore, a critical and clinically oriented evaluation of BBB-targeted nanocarriers is required. This review integrates AD molecular mechanisms, BBB biology, nanocarrier design, therapeutic applications, translational challenges and future directions for next-generation AD nanomedicine.

2. Literature Search Methodology

This manuscript was prepared as a narrative review with a structured literature search approach. Relevant publications were identified using PubMed, Scopus, Web of Science, ScienceDirect, SpringerLink and Google Scholar. Search terms included combinations of "Alzheimer's disease", "blood-brain barrier", "nanocarriers", "nanoparticles", "liposomes", "PLGA nanoparticles", "solid lipid nanoparticles", "nanostructured lipid carriers", "exosomes", "transferrin receptor", "lactoferrin", "ApoE", "intranasal delivery", "RNA delivery", "theranostics" and "clinical translation". Emphasis was placed on original research and reviews published from 2015 to 2026, while seminal older literature was included where necessary for core mechanistic concepts.

Studies were considered relevant if they discussed AD pathology, BBB physiology, brain-targeted delivery systems, nanocarrier design, preclinical efficacy or translational issues. Articles focusing exclusively on non-neurological nanomedicine without BBB relevance were excluded. The final reference list should be checked and expanded according to the target journal guidelines before submission.

Table 1. Search strategy used for manuscript preparation.

Database	Main search terms	Selection focus
PubMed	Alzheimer disease AND nanoparticle; blood-brain barrier AND nanocarrier	Mechanistic and biomedical literature
Scopus	BBB-targeted drug delivery; nanomedicine Alzheimer	Review and original studies
Web of Science	Brain targeting nanoparticles; receptor-mediated transcytosis	Citation-rich studies
ScienceDirect/SpringerLink	Liposomes, PLGA, SLN, exosome, theranostics	Drug-delivery platforms
ClinicalTrials.gov/WHO resources	Dementia, AD therapies, clinical translation	Clinical and epidemiological context

3. Molecular Pathogenesis of Alzheimer's Disease

3.1 Amyloidogenic processing and Aβ toxicity

The amyloid cascade hypothesis proposes that abnormal cleavage of amyloid precursor protein (APP) initiates a pathogenic sequence culminating in synaptic failure and neuronal degeneration. APP can undergo a non-amyloidogenic pathway through α-secretase cleavage or an amyloidogenic pathway involving β-site APP cleaving enzyme 1 (BACE1) followed by γ-secretase. The latter route generates Aβ peptides, particularly Aβ42, which aggregates more readily than Aβ40. Soluble Aβ oligomers are considered especially toxic because they interfere with synaptic plasticity, impair long-term potentiation, disturb calcium homeostasis, promote oxidative stress and activate glial inflammatory responses.

Aβ plaques are a major histopathological hallmark; however, plaque burden alone does not fully explain cognitive impairment. This observation has shifted attention toward soluble oligomers, impaired Aβ clearance, vascular deposition and interactions between amyloid and tau pathology. BBB dysfunction also contributes by reducing clearance of Aβ from the brain through low-density lipoprotein receptor-related protein 1 (LRP1) pathways and by increasing influx through receptors such as RAGE under inflammatory conditions.

3.2 Tau hyperphosphorylation and neurofibrillary tangles

Tau is a microtubule-associated protein that stabilizes axonal microtubules. In AD, abnormal phosphorylation mediated by kinases including glycogen synthase kinase-3β, cyclin-dependent kinase 5 and mitogen-activated protein kinases decreases tau binding to microtubules and

promotes aggregation into paired helical filaments and neurofibrillary tangles. Tau pathology correlates more closely with neurodegeneration and cognitive decline than amyloid plaque load.

Therapeutic strategies targeting tau include kinase inhibition, tau aggregation blockers, microtubule stabilizers, anti-tau antibodies and nucleic acid approaches designed to reduce tau expression. Delivery remains a major barrier because many tau-directed drugs are peptides, antibodies or nucleic acids with poor BBB permeability. Nanocarriers capable of neuronal targeting may therefore be important for future anti-tau therapy.

3.3 Neuroinflammation and glial activation

Neuroinflammation is no longer viewed only as a secondary response but as an active driver of AD progression. Microglia respond to Aβ, tau aggregates and neuronal debris by adopting complex activation states. Early microglial activation may support phagocytosis and clearance, whereas chronic activation promotes release of inflammatory cytokines, chemokines, complement proteins, nitric oxide and reactive oxygen species. Astrocytes also become reactive and contribute to inflammatory amplification, glutamate dysregulation and BBB changes.

Genetic studies implicating TREM2, CD33, CR1 and other immune-related genes support the role of innate immunity in AD susceptibility. Nanocarriers can be engineered to deliver anti-inflammatory drugs, siRNA or antioxidant molecules to activated microglia and astrocytes. However, excessive suppression of microglial function may impair Aβ clearance, indicating the need for balanced immunomodulation rather than nonspecific anti-inflammatory therapy.

3.4 Oxidative stress and mitochondrial dysfunction

The brain consumes a high proportion of body oxygen and contains abundant lipids, making it highly vulnerable to oxidative damage. In AD, Aβ accumulation, mitochondrial dysfunction, metal ion imbalance, inflammation and impaired antioxidant defences increase reactive oxygen and nitrogen species. Oxidative stress damages lipids, proteins and nucleic acids, disrupts synaptic function and accelerates neuronal death.

Mitochondrial dysfunction contributes to reduced ATP production, calcium imbalance, increased ROS generation and activation of apoptotic pathways. Aβ and tau can interfere with mitochondrial trafficking and respiratory chain function. Nanocarriers designed to deliver antioxidants, mitochondrial protectants and natural polyphenols may reduce oxidative injury, although successful translation requires improved bioavailability and brain exposure.

3.5 Synaptic dysfunction, cholinergic deficit and vascular contribution

Synaptic loss is one of the strongest correlates of cognitive decline. Aβ oligomers disrupt synaptic receptors, impair neurotransmission and alter dendritic spine structure. Cholinergic neurons in the basal forebrain are particularly affected, leading to acetylcholine deficiency and providing the rationale for cholinesterase inhibitors. Vascular dysfunction, cerebral amyloid angiopathy, BBB leakage and impaired perfusion further contribute to disease progression.

A complete therapeutic strategy should therefore address neuronal, glial and vascular compartments. Nanocarriers that can target the neurovascular unit and release drugs in response to pathological stimuli may provide a more integrated approach than conventional single-target treatments.

Table 2. Molecular mechanisms and therapeutic targets in Alzheimer's disease.

Pathway	Key molecules	Pathological consequence	Nanomedicine opportunity
Amyloidogenesis	APP, BACE1, γ-secretase, Aβ42	Synaptic dysfunction and plaque deposition	BACE1 siRNA, anti-Aβ peptides, Aβ-binding nanoparticles
Tau pathology	Tau, GSK-3β, CDK5	Microtubule instability and tangles	Anti-tau antibodies, tau siRNA, kinase inhibitor delivery
Neuroinflammation	TREM2, CD33, TNF-α, IL-1β, complement	Chronic glial activation and neuronal injury	Microglia-targeted anti-inflammatory nanocarriers
Oxidative stress	ROS, RNS, metal ions	Lipid, DNA and protein damage	Antioxidant and polyphenol nanocarriers
Mitochondrial dysfunction	Complex I-IV dysfunction, ATP depletion	Energy failure and apoptosis	Mitochondria-targeted carriers
BBB dysfunction	TJ disruption, efflux pumps, altered LRP1/RAGE	Reduced drug entry and impaired Aβ clearance	Receptor-targeted and biomimetic nanocarriers

4. Blood-Brain Barrier Structure, Physiology and Dysfunction in AD

The BBB is formed by non-fenestrated brain microvascular endothelial cells connected by tight

junctions and supported by pericytes, astrocytic end-feet, basement membrane, neurons and extracellular matrix. These elements collectively constitute the neurovascular unit. Tight junction proteins such as claudin-5, occludin and zonula occludens proteins restrict paracellular diffusion. The endothelial cells also express efflux transporters, including P-glycoprotein and breast cancer resistance protein, which actively remove many drugs from the brain.

BBB transport is highly selective. Small lipophilic molecules may cross by passive diffusion if they possess favourable physicochemical properties. Glucose, amino acids and essential nutrients enter through carrier-mediated transporters such as GLUT1 and LAT1. Larger endogenous proteins including transferrin and insulin cross through receptor-mediated transcytosis. Cationic ligands can use adsorptive-mediated transcytosis. Immune cells may traffic across the barrier under inflammatory conditions.

In AD, BBB function is altered by ageing, inflammation, vascular injury, pericyte loss, oxidative stress and amyloid deposition. BBB disruption can increase leakage of plasma proteins, disturb ionic homeostasis, activate glial cells and impair Aβ clearance. Importantly, BBB alterations are not uniform throughout disease progression. Early AD may show subtle transporter changes, while advanced disease can involve structural leakage and inflammatory remodelling. Nanocarriers must therefore be designed with disease stage and patient heterogeneity in mind.

Table 3. BBB transport pathways relevant to nanocarrier design.

Transport pathway	Biological basis	Nanocarrier strategy	Limitations
Passive diffusion	Dependent on lipophilicity and molecular size	Small lipidic carriers and prodrug loading	Limited for biologics and hydrophilic drugs
Carrier-mediated transport	Nutrient transporters such as GLUT1/LAT1	Ligand or substrate-mimetic carriers	Competition with endogenous substrates
Receptor-mediated transcytosis	TfR, insulin receptor, LRP1 and related receptors	Ligand-conjugated nanoparticles	Receptor saturation and off-target uptake
Adsorptive-mediated transcytosis	Electrostatic interaction with endothelial membrane	Cationic liposomes or CPP-functionalized particles	Potential toxicity and nonspecific binding
Cell-mediated transport	Immune cell trafficking	Macrophage or monocyte-associated delivery	Inflammation dependence and complexity
Intranasal nose-to-brain transport	Olfactory and trigeminal pathways	Mucoadhesive nanoparticles and nanoemulsions	Variable deposition and dose limitation

5. BBB-Targeting Strategies for Nanocarriers

5.1 Receptor-mediated transcytosis

Receptor-mediated transcytosis is one of the most widely explored strategies for brain targeting. Transferrin receptor, insulin receptor, lactoferrin receptor, LRP1 and LDL receptor family members are attractive because they are expressed on brain endothelial cells and naturally transport essential ligands. Nanocarriers decorated with transferrin, lactoferrin, ApoE-derived peptides or specific antibodies can bind these receptors and undergo vesicular transport across endothelial cells. The major design challenge is to achieve sufficient affinity for transport without causing receptor trapping or peripheral sequestration.

5.2 Cell-penetrating peptides and peptide ligands

Cell-penetrating peptides such as TAT, penetratin and angiopep-2 can enhance cellular uptake and BBB penetration. RVG peptide, derived from rabies virus glycoprotein, has been used for neuronal targeting. Peptide-modified nanocarriers can improve brain uptake of genes, proteins and hydrophobic drugs. However, cationic peptides may increase nonspecific tissue binding and toxicity; therefore, charge density, peptide orientation and linker chemistry must be optimized.

5.3 Intranasal and mucosal targeting

Intranasal delivery bypasses first-pass metabolism and may provide direct access to the brain through olfactory and trigeminal pathways. This route is attractive for AD because it is non-invasive and suitable for chronic treatment. Mucoadhesive nanoparticles, nanoemulsions and in situ gels can improve residence time in the nasal cavity. Nevertheless, mucociliary clearance, enzymatic degradation, limited dose volume and inter-individual variability remain important limitations.

5.4 Biomimetic and cell membrane-coated systems

Biomimetic nanocarriers use biological membranes or natural vesicles to improve circulation, reduce immune recognition and enable cell-specific interactions. Red blood cell membrane coating prolongs circulation, leukocyte membrane coating may target inflamed endothelium, and exosomes naturally participate in intercellular communication. These systems are promising for AD, particularly where inflammation and BBB dysfunction are present, but batch consistency, cargo loading and source-cell safety require careful control.

Table 4. BBB-targeting ligands and design considerations.

Ligand/approach	Target	Typical nanocarrier use	Key concern
Transferrin/anti-TfR antibody	Transferrin receptor	Liposomes, polymeric nanoparticles, antibody-drug systems	Receptor saturation and peripheral uptake
Lactoferrin	Lactoferrin receptor	PLGA, SLN and liposomes	Variable receptor expression
ApoE/ApoE peptides	LDL receptor family	Polysorbate-coated or ApoE-decorated nanoparticles	Lipoprotein competition
Angiopep-2	LRP1-related transport	Polymeric nanoparticles and peptides	Affinity optimization needed
TAT/penetratin	Membrane translocation	Gene and peptide delivery	Nonspecific cationic toxicity
RVG peptide	Nicotinic acetylcholine receptor-related neuronal targeting	siRNA and exosome delivery	Species and model dependence
Intranasal mucoadhesion	Olfactory/trigeminal route	Chitosan nanoparticles, nanoemulsions	Dose and deposition limitations

6. Nanocarriers for Alzheimer's Disease Therapy

6.1 Liposomes

Liposomes are spherical vesicles composed of phospholipid bilayers surrounding aqueous compartments. They can carry hydrophilic drugs in the core and hydrophobic drugs within the membrane. Their biocompatibility and established clinical use make them attractive for brain drug delivery. PEGylation can prolong circulation, whereas ligand conjugation can promote receptor-mediated BBB transport.

In AD research, liposomes have been investigated for delivery of cholinesterase inhibitors, antioxidants, curcumin, resveratrol, peptides and nucleic acids. Multifunctional liposomes can combine BBB-targeting ligands with Aβ-binding moieties or imaging agents. Major limitations include possible leakage, oxidation of lipids, complement activation and manufacturing complexity.

6.2 Polymeric nanoparticles

Polymeric nanoparticles are commonly prepared from biodegradable polymers such as PLGA, PLA, polycaprolactone, chitosan and PEG-containing copolymers. These systems provide controlled release, protection of unstable drugs and versatile surface modification. PLGA nanoparticles are especially attractive because PLGA is biodegradable and widely used in approved drug products.

For AD, polymeric nanoparticles have been used to deliver curcumin, quercetin, memantine, tacrine, anti-inflammatory drugs, siRNA and peptides. Surface modification with polysorbate 80, transferrin, lactoferrin, ApoE peptides or angiopep-2 can improve brain uptake. However, residual solvents, burst release, acidic degradation products and scale-up reproducibility must be addressed.

6.3 Solid lipid nanoparticles and nanostructured lipid carriers

Solid lipid nanoparticles (SLNs) contain a solid lipid core stabilized by surfactants. They offer good tolerability, controlled release and protection of lipophilic drugs. Nanostructured lipid carriers (NLCs) combine solid and liquid lipids, producing an imperfect matrix that improves drug loading and reduces expulsion during storage.

SLNs and NLCs are particularly useful for lipophilic anti-AD agents, including donepezil, rivastigmine, curcumin and resveratrol. They can be administered orally, intravenously or intranasally. Their lipid composition may promote interaction with lipoprotein-mediated pathways. Important challenges include polymorphic transitions, physical stability and surfactant-related toxicity.

6.4 Dendrimers and polymeric micelles

Dendrimers are highly branched nanoscale macromolecules with controlled architecture and multiple terminal groups. They can carry drugs through encapsulation or covalent conjugation and can be modified with targeting ligands. PAMAM dendrimers have been studied for anti-inflammatory and gene-delivery applications in neurological disorders.

Polymeric micelles self-assemble from amphiphilic block copolymers and are useful for solubilizing hydrophobic drugs. Their small size and PEG corona may favour prolonged circulation. In AD, micelles can improve delivery of polyphenols and hydrophobic neuroprotective agents. Their limitations include dilution-induced dissociation and limited drug-loading for some cargos.

6.5 Exosomes and extracellular vesicles

Exosomes are nanosized extracellular vesicles secreted by cells and involved in intercellular communication. They possess natural membranes, intrinsic biocompatibility and the ability to carry proteins, lipids, mRNA, miRNA and siRNA. Exosomes can cross biological barriers and may be engineered with targeting peptides such as RVG for neuronal delivery.

In AD, exosomes are being investigated for delivery of siRNA against BACE1, anti-inflammatory miRNAs, antioxidant enzymes and neuroprotective proteins. They may also serve as biomarkers because neuronal exosomes can carry disease-associated proteins. However, therapeutic exosomes face major challenges including purification, heterogeneity, cargo loading, potency assays, storage and regulatory classification.

6.6 Inorganic and hybrid nanoplatforms

Gold nanoparticles, iron oxide nanoparticles, mesoporous silica nanoparticles, carbon-based materials and cerium oxide nanoparticles have been explored for AD diagnosis and therapy. Gold nanoparticles may interact with amyloid aggregation and can be used for imaging or photothermal applications. Iron oxide nanoparticles provide magnetic resonance imaging contrast and magnetic targeting potential. Cerium oxide nanoparticles possess redox activity and may reduce oxidative stress.

Inorganic nanoparticles are useful for theranostics because their optical, magnetic or catalytic properties can be integrated with drug delivery. Nevertheless, long-term accumulation, biodegradability, metal ion release and neurotoxicity require careful evaluation before clinical translation. Hybrid organic-inorganic systems may offer a balanced approach by combining imaging capability with biocompatible coatings.

Table 5. Comparative overview of nanocarriers for AD therapy.

Nanocarrier	Main advantages	Representative cargo	Limitations
Liposomes	Biocompatible; hydrophilic and hydrophobic drug loading; ligand modification	Donepezil, curcumin, peptides, antibodies	Leakage, oxidation, complement activation
Polymeric nanoparticles	Controlled release; biodegradable; versatile surface chemistry	Curcumin, memantine, siRNA, tacrine	Burst release, residual solvent, scale-up
SLNs	Stable lipid matrix; suitable for lipophilic drugs	Rivastigmine, donepezil, resveratrol	Polymorphic transition, limited loading
NLCs	Higher loading than SLNs; reduced drug expulsion	Curcumin, quercetin, anti-inflammatory drugs	Surfactant and stability issues
Dendrimers	Defined architecture; multivalent functionalization	siRNA, anti-inflammatory agents	Generation-dependent toxicity
	ion		
Micelles	Solubilize hydrophobic drugs; small size	Polyphenols, hydrophobic antioxidants	Dilution instability
Exosomes	Natural BBB crossing; biological communication	miRNA, siRNA, proteins	Heterogeneity and manufacturing control
Inorganic nanoparticles	Imaging, redox or magnetic properties	Theranostic agents and antioxidants	Persistence and long-term safety

7. Therapeutic Cargos Delivered by BBB-Targeted Nanocarriers

7.1 Anti-amyloid and anti-tau strategies

Nanocarriers can deliver molecules that inhibit Aβ production, prevent aggregation, promote clearance or neutralize toxic oligomers. BACE1 inhibitors, γ-secretase modulators, anti-Aβ peptides, antibodies and Aβ-binding molecules have been incorporated into nanosystems. Similarly, anti-tau strategies include kinase inhibitors, tau aggregation inhibitors, antibodies and tau-targeted nucleic acids. Delivery systems must ensure sufficient brain exposure while avoiding peripheral toxicity and immune activation.

7.2 Anti-inflammatory and antioxidant therapy

Because neuroinflammation and oxidative stress are central in AD progression, nanocarriers have been used to deliver non-steroidal anti-inflammatory drugs, corticosteroid-like agents, natural antioxidants, antioxidant enzymes and redox-active nanoparticles. Targeting activated microglia or inflamed endothelium may improve efficacy. However, inflammation has both protective and harmful roles, so excessive suppression may be counterproductive.

7.3 Cholinesterase inhibitors and NMDA-modulating agents

Approved symptomatic drugs can benefit from nanocarrier delivery by improving brain exposure, reducing dosing frequency and minimizing peripheral adverse effects. Intranasal nanocarriers of rivastigmine and donepezil have attracted attention because they may increase direct nose-to-brain transport. Such formulations may be useful for chronic symptomatic management but should ideally be combined with disease-modifying strategies.

7.4 Phytochemical-loaded nanocarriers

Curcumin, resveratrol, quercetin, epigallocatechin gallate, berberine and other phytochemicals show antioxidant, anti-inflammatory and anti-amyloid properties. Their major limitations include poor solubility, rapid metabolism, low oral bioavailability and poor BBB penetration. Nanoformulation improves solubility, stability, brain delivery and controlled release, making

phytochemical nanomedicine a highly active area in AD research.

7.5 RNA and gene-based therapy

RNA therapeutics can silence genes involved in AD pathology, including BACE1, APP, tau and inflammatory mediators. Nanocarriers protect siRNA, miRNA and antisense oligonucleotides from nuclease degradation and facilitate cellular uptake. Exosomes, lipid nanoparticles and polymeric nanoparticles are particularly relevant. However, off-target effects, immune stimulation, endosomal escape and long-term safety remain important challenges.

Table 6. Phytochemicals and natural compounds investigated for AD nanomedicine.

Compound	Major mechanism	Nanoformulation rationale	Expected benefit
Curcumin	Anti-amyloid, antioxidant, anti-inflammatory	Improves solubility and BBB delivery	Reduced Aβ toxicity and oxidative stress
Resveratrol	SIRT1 activation, antioxidant, anti-inflammatory	Enhances stability and brain exposure	Mitochondrial and synaptic protection
Quercetin	ROS scavenging and anti-inflammatory activity	Improves bioavailability	Protection against Aβ-induced toxicity
EGCG	Anti-aggregation and antioxidant effect	Improves stability	Modulation of amyloid aggregation
Berberine	Anti-inflammatory, metabolic and cholinergic effects	Improves absorption and brain targeting	Multi-target neuroprotection
Huperzine A	Acetylcholinesterase inhibition	Controlled delivery	Symptomatic cognitive support

Table 7. RNA and gene-based nanotherapeutic strategies.

Cargo	Target	Preferred carrier	Key translational issue
siRNA	BACE1, APP, tau, inflammatory genes	Lipid nanoparticles, polymeric nanoparticles, exosomes	Endosomal escape and off-target silencing
miRNA mimics/inhibitors	Neuroinflammation, synaptic and amyloid pathways	Exosomes and cationic nanocarriers	Pleiotropic effects
Antisense oligonucleotides	Tau or APP-related transcripts	Ligand-modified nanoparticles	Repeated dosing and safety
CRISPR/Cas systems	Disease-associated genes	Lipid/polymeric hybrid systems	Permanent editing risks
mRNA	Neuroprotective proteins or enzymes	Lipid nanoparticles	Transient expression and immunogenicity

8. Theranostic Nanocarriers and Diagnostic Integration

Theranostic nanocarriers combine therapeutic delivery with diagnostic imaging or biomarker detection. This concept is valuable in AD because disease progression is heterogeneous and therapeutic response is difficult to monitor using clinical endpoints alone. Nanoparticles carrying imaging agents can help visualize Aβ plaques, tau pathology, oxidative stress or inflammatory changes while simultaneously delivering therapeutic cargo.

Iron oxide nanoparticles are useful for magnetic resonance imaging, gold nanoparticles for optical and photoacoustic applications, and quantum dots or fluorescent probes for experimental imaging. Mesoporous silica nanoparticles can combine high drug loading with imaging labels. Theranostic platforms may also support personalized medicine by enabling patient stratification, monitoring BBB penetration and evaluating target engagement.

However, theranostic systems are often more complex than simple drug carriers. Their regulatory path is challenging because both diagnostic and therapeutic components must be evaluated. For clinical translation, developers must demonstrate that imaging capability improves treatment decisions and is not merely an experimental add-on.

Table 8. Theranostic nanoplatforms for AD-related applications.

Platform	Diagnostic function	Therapeutic function	Main concern
Iron oxide nanoparticles	MRI contrast	Drug delivery, magnetic targeting	Long-term iron handling and coating stability
Gold nanoparti	Optical/photoacoustic imaging	Anti-aggregati	Persistence and dose-

cles		on or photothermal effects	related toxicity
Mesoporous silica nanoparticles	Fluorescent or MRI labeling	High drug loading and controlled release	Biodegradation and clearance
Quantum dots	Fluorescence imaging	Tracking nanocarrier distribution	Heavy metal toxicity
Cerium oxide nanoparticles	Redox monitoring potential	ROS scavenging	Long-term accumulation
Hybrid lipid-inorganic systems	Multimodal imaging	Combined drug and gene delivery	Manufacturing complexity

9. Clinical Translation, Safety and Regulatory Considerations

The gap between preclinical promise and clinical success is a major issue in brain nanomedicine. Many formulations show encouraging in vitro uptake or animal efficacy but fail to demonstrate clinically meaningful brain exposure or therapeutic benefit. A key problem is overreliance on simplified BBB models that do not reproduce human endothelial phenotype, ageing, disease-associated inflammation or protein corona formation. Future studies should combine validated human cellular models, organ-on-chip systems, quantitative pharmacokinetics and clinically relevant animal models.

Safety evaluation must consider acute and chronic toxicity, complement activation, immunogenicity, neuroinflammation, genotoxicity, reproductive toxicity, biodistribution, clearance and degradation products. The AD population is elderly and often has comorbidities, polypharmacy and vascular disease, making safety margins especially important. Nanocarriers intended for chronic use must demonstrate long-term tolerability.

Manufacturing is another translational bottleneck. Parameters such as particle size, polydispersity, zeta potential, encapsulation efficiency, ligand density, sterility, endotoxin level, residual solvent and batch-to-batch reproducibility must be controlled. Complex biomimetic or exosome systems require robust identity, purity and potency assays. Regulatory agencies increasingly expect quality-by-design approaches and clear justification of critical quality attributes.

Clinical development should not focus only on whether a nanoparticle crosses the BBB. It must also demonstrate target engagement, pharmacodynamic effect, disease-stage suitability and improvement in clinically meaningful outcomes. Biomarkers such as amyloid PET, tau PET, cerebrospinal fluid or plasma p-tau, neurofilament light chain and imaging markers of neuroinflammation may support early-phase trials.

Table 9. Major translational challenges and possible solutions.

Challenge	Impact	Possible solution
Poor model predictability	False-positive preclinical results	Use human BBB models and quantitative in vivo PK
Protein corona formation	Alters targeting and biodistribution	Evaluate in human plasma and aged/disease models
Scale-up variability	Batch inconsistency	Quality-by-design and process analytical controls
Long-term safety	Limits chronic use	Repeated-dose toxicology and neuroimmune monitoring
Ligand density optimization	Receptor trapping or poor transport	Systematic affinity and density studies
Regulatory complexity	Delayed approval	Early regulatory consultation and clear CQA definition
Clinical endpoint sensitivity	Slow disease progression	Use biomarkers and enriched patient selection

10. Artificial Intelligence-Assisted Nanomedicine

Artificial intelligence (AI) and machine learning can accelerate the design of BBB-targeted nanocarriers by analysing multidimensional formulation variables and biological outcomes. Particle size, charge, hydrophobicity, polymer composition, ligand density, drug loading and release kinetics can be correlated with BBB permeability, toxicity and therapeutic response. Predictive models may reduce experimental burden and identify optimal formulation regions.

AI can also support drug repurposing, target discovery, biomarker interpretation and patient stratification. In AD, where disease heterogeneity is substantial, computational tools may help identify which patients are most likely to benefit from anti-amyloid, anti-tau, anti-inflammatory or vascular-targeted nanotherapies. However, AI models require high-quality datasets, standardized experimental reporting and external validation before they can guide clinical decisions.

11. Future Perspectives

Future BBB-targeted nanocarriers for AD should move beyond simple drug encapsulation toward disease-stage-specific, biomarker-guided and multifunctional systems. Early-stage AD may require carriers that enhance Aβ clearance and protect synapses, whereas later stages may require anti-inflammatory, anti-tau and neuroprotective strategies. Personalized approaches based on amyloid status, tau burden, vascular risk, APOE genotype and inflammatory profile may improve therapeutic success.

Biomimetic nanocarriers and engineered exosomes are likely to expand because of their biological compatibility and potential for cell-specific communication. Stimuli-responsive systems that release cargo in response to oxidative stress, enzymes, pH or inflammatory signals may improve local precision. Intranasal nanomedicine may become important for chronic outpatient therapy if reproducible delivery and dosing can be achieved.

For the field to advance, studies must report complete physicochemical characterization, reproducible preparation methods, appropriate controls, quantitative brain biodistribution, therapeutic index and long-term safety. Comparative studies across nanocarrier classes are also needed because many reports evaluate only one formulation without benchmarking against existing delivery platforms.

12. Conclusions

BBB-targeted nanocarriers represent a promising strategy for improving the treatment of Alzheimer's disease. The biological complexity of AD and the restrictive nature of the BBB make conventional drug delivery insufficient for many therapeutic candidates. Nanocarriers can enhance solubility, protect unstable molecules, prolong circulation, promote controlled release and exploit BBB transport pathways. Liposomes, polymeric nanoparticles, lipid nanoparticles, dendrimers, micelles, exosomes and inorganic platforms each offer unique advantages and limitations.

The most promising future systems will likely be multifunctional, biomimetic and guided by disease biology. However, clinical translation requires rigorous validation, scalable manufacturing, long-term safety assessment and demonstration of meaningful clinical benefit. Rather than viewing BBB penetration as the sole objective, next-generation nanomedicine should integrate target engagement, disease-stage specificity, patient stratification and regulatory feasibility. With coordinated advances in neuroscience, formulation science, biomaterials, pharmacokinetics and AI-assisted design, BBB-targeted nanocarriers may contribute significantly to disease-modifying therapy for AD.

Figure Captions

Figure 1. Schematic representation of Alzheimer's disease pathogenesis showing amyloid-beta aggregation, tau hyperphosphorylation, oxidative stress, mitochondrial dysfunction, neuroinflammation, synaptic loss and neuronal death.

Figure 2. Structure of the blood-brain barrier and neurovascular unit, including endothelial cells, tight junction proteins, pericytes, astrocytic end-feet, basement membrane and neurons.

Figure 3. Major BBB transport pathways used by nanocarriers: passive diffusion, carrier-mediated transport, receptor-mediated transcytosis, adsorptive-mediated transcytosis, cell-mediated transport and intranasal nose-to-brain delivery.

Figure 4. Classification of BBB-targeted nanocarriers for AD therapy, including liposomes, polymeric nanoparticles, SLNs, NLCs, dendrimers, micelles, exosomes and inorganic nanoparticles.

Figure 5. Surface-engineered nanocarriers using transferrin, lactoferrin, ApoE, angiopep-2, TAT and RVG ligands for brain targeting.

Figure 6. Theranostic nanocarrier concept integrating BBB transport, therapeutic release, imaging and biomarker-based monitoring.

Figure 7. Clinical translation roadmap for AD nanomedicine from formulation design to physicochemical characterization, preclinical validation, GMP scale-up, regulatory evaluation and clinical trials.

Table 10. List of abbreviations.

Abbreviation	Full form
Aβ	Amyloid-beta
AD	Alzheimer's disease
APP	Amyloid precursor protein
BBB	Blood-brain barrier
BACE1	β-site APP cleaving enzyme 1
CNS	Central nervous system
CPP	Cell-penetrating peptide
EGCG	Epigallocatechin gallate
LRP1	Low-density lipoprotein receptor-related protein 1
NLC	Nanostructured lipid carrier
NFT	Neurofibrillary tangle
PLGA	Poly(lactic-co-glycolic acid)
ROS	Reactive oxygen species
SLN	Solid lipid nanoparticle
TfR	Transferrin receptor

References

1. World Health Organization. Dementia fact sheet. WHO; 2025.
2. Alzheimer's Disease International. Dementia statistics: global prevalence and projections.
3. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science. 2002;297:353-356.
4. Long JM, Holtzman DM. Alzheimer disease: an update on pathobiology and treatment strategies. Cell. 2019;179:312-339.
5. Querfurth HW, LaFerla FM. Alzheimer's disease. N Engl J Med. 2010;362:329-344.

6. Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Mol Med. 2016;8:595-608.
7. Haass C, Selkoe DJ. Soluble protein oligomers in neurodegeneration. Nat Rev Mol Cell Biol. 2007;8:101-112.
8. De Strooper B, Karran E. The cellular phase of Alzheimer's disease. Cell. 2016;164:603-615.
9. Wang Y, Mandelkow E. Tau in physiology and pathology. Nat Rev Neurosci. 2016;17:5-21.
10. Goedert M, Eisenberg DS, Crowther RA. Propagation of tau aggregates and neurodegeneration. Annu Rev Neurosci. 2017;40:189-210.
11. Heneka MT, Carson MJ, El Khoury J, et al. Neuroinflammation in Alzheimer's disease. Lancet Neurol. 2015;14:388-405.
12. Leng F, Edison P. Neuroinflammation and microglial activation in Alzheimer disease. Nat Rev Neurol. 2021;17:157-172.
13. Butterfield DA, Halliwell B. Oxidative stress, dysfunctional glucose metabolism and Alzheimer disease. Nat Rev Neurosci. 2019;20:148-160.
14. Swerdlow RH. Mitochondria and mitochondrial cascades in Alzheimer's disease. J Alzheimers Dis. 2018;62:1403-1416.
15. Hampel H, Mesulam MM, Cuello AC, et al. The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. Brain. 2018;141:1917-1933.
16. Zlokovic BV. The blood-brain barrier in health and chronic neurodegenerative disorders. Neuron. 2008;57:178-201.
17. Sweeney MD, Sagare AP, Zlokovic BV. Blood-brain barrier breakdown in Alzheimer disease. Nat Rev Neurol. 2018;14:133-150.
18. Abbott NJ, Patabendige AAK, Dolman DEM, et al. Structure and function of the blood-brain barrier. Neurobiol Dis. 2010;37:13-25.
19. Daneman R, Prat A. The blood-brain barrier. Cold Spring Harb Perspect Biol. 2015;7:a020412.
20. Pardridge WM. Blood-brain barrier drug delivery. Biochim Biophys Acta. 2012;1818:1955-1962.
21. Pardridge WM. Delivery of biologics across the blood-brain barrier with molecular Trojan horse technology. BioDrugs. 2017;31:503-519.
22. Saraiva C, Praça C, Ferreira R, et al. Nanoparticle-mediated brain drug delivery: overcoming blood-brain barrier to treat neurodegenerative diseases. J Control Release. 2016;235:34-47.
23. Teleanu DM, Chircov C, Grumezescu AM, et al. Blood-brain delivery methods using nanotechnology. Pharmaceutics. 2018;10:269.
24. Wohlfart S, Gelperina S, Kreuter J. Transport of drugs across the blood-brain barrier by nanoparticles. J Control Release. 2012;161:264-273.
25. Kreuter J. Drug delivery to the central nervous system by polymeric nanoparticles. Adv Drug Deliv Rev. 2001;47:65-81.
26. Torchilin VP. Multifunctional nanocarriers. Adv Drug Deliv Rev. 2012;64:302-315.
27. Johnsen KB, Burkhart A, Thomsen LB, et al. Targeting the transferrin receptor for brain drug delivery. Prog Neurobiol. 2019;181:101665.
28. Pulgar VM. Transcytosis to cross the blood brain barrier, new advancements and challenges. Front Neurosci. 2019;12:1019.
29. Ulbrich K, Hekmatara T, Herbert E, Kreuter J. Transferrin- and transferrin-receptor-antibody-modified nanoparticles enable drug delivery across the BBB. Eur J Pharm Biopharm. 2009;71:251-256.
30. Demeule M, Régina A, Ché C, et al. Identification and design of peptides as a new drug delivery system for the brain. J Pharmacol Exp Ther. 2008;324:1064-1072.
31. Kumar P, Wu H, McBride JL, et al. Transvascular delivery of small interfering RNA to the central nervous system. Nature. 2007;448:39-43.
32. Alvarez-Erviti L, Seow Y, Yin H, et al. Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes. Nat Biotechnol. 2011;29:341-345.
33. Kooijmans SAA, Schiffelers RM, Zarovni N, Vago R. Modulation of tissue tropism and biological activity of exosomes. J Control Release. 2016;224:77-85.
34. Batrakova EV, Kim MS. Using exosomes, naturally-equipped nanocarriers, for drug delivery. J Control Release. 2015;219:396-405.
35. Gao H. Progress and perspectives on targeting nanoparticles for brain drug delivery. Acta Pharm Sin B. 2016;6:268-286.
36. Kabanov AV, Gendelman HE. Nanomedicine in the diagnosis and therapy of neurodegenerative disorders. Prog Polym Sci. 2007;32:1054-1082.
37. Massart R, Guilloteau D, Chalon S. Nanoparticles for brain drug delivery in neurodegenerative disorders. Curr Pharm Des. 2012;18:293-307.
38. Patel T, Zhou J, Piepmeier JM, Saltzman WM. Polymeric nanoparticles for drug delivery to the central nervous system. Adv Drug Deliv Rev. 2012;64:701-705.
39. Misra A, Ganesh S, Shahiwala A, Shah SP. Drug delivery to the central nervous system: a review. J Pharm Pharm Sci. 2003;6:252-273.
40. Garcia-Garcia E, Andrieux K, Gil S, Couvreur P. Colloidal carriers and blood-brain barrier translocation. Int J Pharm. 2005;298:274-292.
41. Tiwari S, Atluri V, Kaushik A, Yndart A, Nair M. Alzheimer's disease: pathogenesis, diagnostics and therapeutics. Int J Nanomedicine. 2019;14:5541-5554.

42. Pinheiro RG, Granja A, Loureiro JA, Pereira MC, Pinheiro M. Lipid nanoparticles for targeted brain drug delivery. Nanomedicine. 2020;15:2553-2571.
43. Müller RH, Mäder K, Gohla S. Solid lipid nanoparticles for controlled drug delivery. Eur J Pharm Biopharm. 2000;50:161-177.
44. Müller RH, Radtke M, Wissing SA. Nanostructured lipid matrices for improved microencapsulation of drugs. Int J Pharm. 2002;242:121-128.
45. Mehnert W, Mäder K. Solid lipid nanoparticles: production, characterization and applications. Adv Drug Deliv Rev. 2001;47:165-196.
46. Kaur IP, Bhandari R, Bhandari S, Kakkar V. Potential of solid lipid nanoparticles in brain targeting. J Control Release. 2008;127:97-109.
47. Yang H. Nanoparticle-mediated brain-specific drug delivery, imaging, and diagnosis. Pharm Res. 2010;27:1759-1771.
48. Mohs AM, Provenzale JM. Applications of nanotechnology to imaging and therapy of brain tumors. Neuroimaging Clin N Am. 2010;20:283-292.
49. Calvo P, Gouritin B, Chacun H, et al. Long-circulating PEGylated polycyanoacrylate nanoparticles as new drug carrier for brain delivery. Pharm Res. 2001;18:1157-1166.
50. Lockman PR, Mumper RJ, Khan MA, Allen DD. Nanoparticle technology for drug delivery across the BBB. Drug Dev Ind Pharm. 2002;28:1-13.
51. Nowacek AS, Miller RL, McMillan J, et al. NanoART synthesis, characterization, uptake, release and toxicology for human monocyte-macrophage drug delivery. Nanomedicine. 2009;4:903-917.
52. Fornaguera C, García-Celma MJ. Personalized nanomedicine: a revolution at the nanoscale. J Pers Med. 2017;7:12.
53. Muthu MS, Singh S. Targeted nanomedicines: effective treatment modalities for cancer, AIDS and brain disorders. Nanomedicine. 2009;4:105-118.
54. Mishra V, Mahor S, Rawat A, et al. Targeted brain delivery of AZT via transferrin anchored pegylated albumin nanoparticles. J Drug Target. 2006;14:45-53.
55. Wilson B, Samanta MK, Santhi K, et al. Poly(n-butylcyanoacrylate) nanoparticles coated with polysorbate 80 for the targeted delivery of rivastigmine into the brain. Brain Res. 2008;1200:159-168.
56. Wilson B, Samanta MK, Santhi K, et al. Targeted delivery of tacrine into the brain with polysorbate 80-coated poly(n-butylcyanoacrylate) nanoparticles. Eur J Pharm Biopharm. 2008;70:75-84.
57. Kuo YC, Chen HH. Effect of nanoparticulate polybutylcyanoacrylate and methylmethacrylate-sulfopropylmethacrylate on delivery of zidovudine across the BBB. Colloids Surf B Biointerfaces. 2006;50:7-15.
58. Kuo YC, Chung JF. Physicochemical properties of nevirapine-loaded solid lipid nanoparticles and nanostructured lipid carriers. Colloids Surf B Biointerfaces. 2011;83:299-306.
59. Kannan RM, Nance E, Kannan S, Tomalia DA. Emerging concepts in dendrimer-based nanomedicine. J Intern Med. 2014;276:579-617.
60. Nance E, Porambo M, Zhang F, et al. Systemic dendrimer-drug treatment of ischemia-induced neonatal white matter injury. J Control Release. 2015;214:112-120.
61. Gendelman HE, Mosley RL, Boska MD, et al. The promise of nanoformulated neuroprotective agents in neurodegenerative disease. Nanomedicine. 2015;11:751-767.
62. Agrawal M, Ajazuddin, Tripathi DK, et al. Recent advancements in liposomes targeting strategies to cross BBB for CNS disorders. J Control Release. 2017;260:61-77.
63. Kumar A, Chen F, Mozhi A, et al. Innovative pharmaceutical development based on unique properties of nanoscale delivery formulation. Nanoscale. 2013;5:8307-8325.
64. Gao H, Pang Z, Jiang X. Targeted delivery of nano-therapeutics for major disorders of the central nervous system. Pharm Res. 2013;30:2485-2498.
65. Zhang TT, Li W, Meng G, et al. Strategies for transporting nanoparticles across the blood-brain barrier. Biomater Sci. 2016;4:219-229.
66. Liu J, et al. The blood-brain barriers: novel nanocarriers for central nervous system drug delivery. J Nanobiotechnology. 2025.
67. Kochman U, et al. Targeted nanoparticles for drug delivery across the blood-brain barrier in early and late stages of Alzheimer's disease: a review. 2025.
68. Wang K, et al. Nanocarrier-based targeted drug delivery for Alzheimer's disease. Front Pharmacol. 2025.
69. An L, et al. Nanocarriers based therapy and diagnosis of brain diseases. Sci Technol Adv Mater. 2025.
70. Nichols E, Steinmetz JD, Vollset SE, et al. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050. Lancet Public Health. 2022;7:e105-e125.
71. Cummings J, Lee G, Zhong K, Fonseca J, Taghva K. Alzheimer's disease drug development pipeline. Alzheimers Dement (N Y). 2024.
72. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. N Engl J Med. 2023;388:9-21.
73. Sims JR, Zimmer JA, Evans CD, et al. Donanemab in early symptomatic Alzheimer disease. JAMA. 2023;330:512-527.
74. Mintun MA, Lo AC, Duggan Evans C, et al. Donanemab in early Alzheimer's disease. N Engl J Med. 2021;384:1691-1704.
75. Budd Haeberlein S, Aisen PS, Barkhof F, et al. Two randomized phase 3 studies of aducanumab in early

Alzheimer's disease. J Prev Alzheimers Dis. 2022;9:197-210.
76. Karran E, De Strooper B. The amyloid hypothesis in Alzheimer disease: new insights from new therapeutics. Nat Rev Drug Discov. 2022;21:306-318.
77. Knopman DS, Perlmutter JS. Prescribing antiamyloid monoclonal antibodies for Alzheimer disease: safety and ethical considerations. Neurology. 2021;97:773-781.
78. Jack CR Jr, Bennett DA, Blennow K, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. Alzheimers Dement. 2018;14:535-562.
79. Palmqvist S, Janelidze S, Quiroz YT, et al. Discriminative accuracy of plasma phospho-tau217 for Alzheimer disease. JAMA. 2020;324:772-781.